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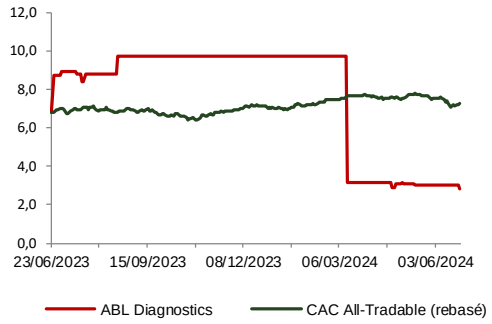
ABL Diagnostics

Recommendation	**1. Strong Buy**
Closing Price on 25 June 2024	**€ 2.80**
Target price	**€ 6.01 (+114.7%)**

Market data	
Reuters / Bloomberg ticker	AB-FR.PA / AB:FP
Market capitalisation (€m)	45.1
Enterprise value (€m)	44.5
Free Float (€m)	13.64 (30.2 %)
Number of shares	16 114 656
Daily volume	€ 416
Capital turnover rate (1 year)	0.13%
High (52 weeks)	€ 9.70
Low (52 weeks)	€ 2.80

Performances	1 month	6 months	12 months
Absolute perf.	-1.3%	-69.1%	-58.8%



Current shareholding structure

ABL SA : 99,27% ; ABL Dx : -% ; Other Shareholders : 0,73%

Agenda

A new era

By positioning itself in growth markets such as genotyping and microbiology, ABL Diagnostics offers an attractive investment opportunity to enter the field of high value-added diagnostics with a 100% integrated company.

With its scientifically powerful platform...

...DeepChek® technology platform, ABL Diagnostics has developed a range of innovative diagnostic tests targeting multiple infections. These tests are used routinely in numerous healthcare and research institutions. ABL Diagnostics has signed several strategic and distribution agreements for development and marketing in numerous countries.

...combined with IT dashboards...

...a range of digital solutions for aggregating and interpreting viral mutation data, combining proprietary software (DeepChek®, ViroScore®) and external, non-proprietary software for analyzing data from diagnostic test kits and integrating them into patient records.

...addressing a growing market...

...as the in vitro diagnostics market, and molecular diagnostics in particular, continues to post sustained growth rates over the next few years. In this competitive market, where the top 7 players monopolize 92% of revenues, ABL can leverage its first-class product offerings in targeted/niche disease contexts (e.g. enteric or respiratory diseases) to increase its market share. Sales growth should be driven by geographic expansion (USA, Europe and Asia), new products (development pipeline, new approvals) and expansion of the installed base (new high-volume sites, new generation instrument).

...ABL Diagnostics develops and launches new products ...

...because it is important for this innovative company to offer products that differentiate it and position it as a leading player in genetic diagnostics. One example of this is the SNG preparation libraries that ABL markets to organizations wishing to carry out high-throughput sequencing.

An attractive risk profile in a highly innovative company

The company's recent growth has been achieved at a sustained pace (sales CAGR of 190% over the 2019-2023 period), and we believe that its growth trajectory is only just beginning. In a market looking for innovation, the combination of the company's proprietary genotyping tests with its software capabilities, as well as its excellent value proposition, make ABL Diagnostics a real investment opportunity.

We initiate coverage of the company with a strong Buy opinion and a price target of €6.01.

Key figures

	2022	2023E	2024E	2025E	2026E
Sales (€m)	8.75	5.61	6.3	8.52	12.74
Change (%)	*39,5%*	*-35,8%*	*12,3%*	*49,5%*	*38,7%*
EBITDA (€m)*	2.68	0.5	0.98	2.01	2.57
EBIT (€m)*	2.12	-0.66	-0.29	3.53	4.96
Ebit margin (%)	24,2%	-11,7%	-4,6%	41,5%	38,9% #
Net profit gp sh. (€m)	2.43	-0.38	-0.01	3.81	5.23
Net margin (%)	27,8%	-6,7%	-0,2%	44,7%	41,1%
EPS	0.02	0.05	-0.02	0	0.24

Ratios

	2022	2023E	2024E	2025E	2026E
EV / Sales	10.4	16.3	14.8	11.3	7.6
EV / EBITDA*	34.1	183.5	95.6	48	37.8
EV / EBIT*	43.2	-139.1	-319.2	27.3	19.6
P / E	122.4	54.1	-120.1	-3949.5	11.8
Gearing (%)	0.1	-0.1	0	0.1	0
Net debt / EBITDA*	-17.3	-92.9	-49.5	-25.5	-20.3
ROCE (%)	0,0	0	0	0.4	0.5

Company presentation

A high level of integration that...

ABL Diagnostics (ABL Dx) is a French molecular diagnostics company specializing in genotyping test kits for infectious diseases. For its proprietary tests, ABL Diagnostics integrates the entire process from R&D through development, manufacturing, support, regulatory affairs, reimbursement, and marketing.

... generates a strong value proposition...

By addressing the infectious diseases market, ABL Diagnostics, with its genotyping tests using the full range of currently available technologies (Sanger, SNG...), has a strong value proposition which should enable the company to grow faster than its reference market. Our forecasts show sales growth of % between 2024 and 2029. This growth should be fueled by increasing demand for genetic information in both infectiology and oncology, population shifts, and the wider adoption of SNG.

...thanks in particular to operational leverage...

The business model adopted by ABL Diagnostics enables it to supply only consumables and software, which have and should continue to have high margins. Moreover, it is not impossible that as business grows, the company will be able to achieve economies of scale or develop higher-margin products.

... and diversified distribution...

Thanks to the combination of its direct sales model and indirect sales through independent local distributors, ABL Diagnostics is present in more markets worldwide. What's more, ABL's proximity to its customers enables it to offer "up-selling" opportunities (e.g. bookshops for SNG).

...in the markets with the greatest appetite for molecular diagnostics.

In addition to its "domestic" European market, ABL Diagnostics is targeting the US market (40% of global IVD) and China, which is showing strong growth rates for genomics activities.

SWOT

Strengths	Weaknesses
- Original, proprietary technologies and innovative products; - Stable, committed management and scientific teams; - First-rate partnerships (Qiagen, ThermoFisher, Interlux, Evolve...).	- Limited self-financing capacity; - Cash flow: visibility
Opportunities	**Threats**
Large, structurally growing markets; - Real medical needs in infectious diseases; - Differentiation of ABL Dx tests; - Barriers to entry for innovative treatments in the sector; - Rapid development of SNG.	- Alternative techniques ; - Very active competition in the molecular Dx field; - Restrictive reimbursement policy and regulatory aspects.

Valuation methods

We used several methods to value ABL Diagnostics. First of all, we valued the most commercially advanced projects, then we added up the parts. Then we used a DCF and stock market comparable.

Risk-adjusted NPV by project (rNPV)

Our valuation using the rNPV model is based on the base scenario, which values all the company's projects at €6.94/share.

DCF of the entire portfolio

Discounted free cash flow, with a weighted average cost of funds of 12%, values the stock at €11,72/share.

Stock market comparable

After composing two samples, one of "Small Cap" stocks and the other of higher capitalizations, all active in the IVD and molecular IVD sectors. The "SC" multiples approach results in a valuation of €3.29 per share. The "LC" multiples approach results in a valuation of €2.09 per share.

Price target

Based on these methods, and for a base case scenario, a price target of €6.01 and a Strong Buy recommendation.

Summary and Opinion

It's a real opportunity to position ourselves today in ABL Diagnostics, first and foremost because the company has a platform of diagnostic tests that are particularly relevant for monitoring and identifying drug resistance in viruses and bacteria associated with infectious diseases.

ABL Diagnostics genotyping tests are now routinely used in some sixty countries worldwide, providing customers with innovative, rapid and more cost-effective solutions than traditional methods. By mastering several sequencing technologies, ABL Diagnostics is able to adapt to the needs of its customers.

This agility contributes to the longevity of the contracts signed by the company, since we have been in business for over ten years. ABL's excellent reputation is backed up by a particularly relevant value proposition, marked by a strong capacity for innovation.

This is why we believe that its risk profile is favorable, as ABL Diagnostics is now an integrated company, from the design, manufacture, and marketing of its tests, and can therefore spread risk factors over the entire value-creation chain.

In addition, dependence on SARS-Cov-2, which has been the lot of the entire sector, has been significantly reduced, since over 90% of ABL Diagnostics' product mix does not include Covid products.

This is why we are initiating coverage of ABL Diagnostics with a Strong Buy rating and a price target of €6.01 per share, representing a significant upside potential of +114.7 %.

1 Investment thesis

ABL Diagnostics: a natural focus on infectious diseases...

ABL Diagnostics (ABLD) is a molecular diagnostics company that designs, develops, and markets diagnostic test kits, software, and instrumentation. The company has deliberately chosen since its creation to focus on infectious diseases and more particularly the detection of the Human Immunodeficiency Virus (HIV). By developing a recognized competence in the detection of mutated or non-mutated sequences of nucleotide acids (RNA and DNA) and validated by CE marking and the ISO 13485 standard, ABLD offers a true DeepChek® platform for microbiological genotyping. The company is able to market its genotyping tests for different families of viruses or bacteria from HIV to pathogens responsible for respiratory diseases (SARS-CoV-2, TB, RSV, INFLUENZA), urological diseases with BKV, including Hepatitis B, C and D VIRUSES (HBV, HCV, HDV), herpes simplex viruses (HSV), Cytomegalovirus (CMV), bacterial diseases with the measurement of 16s RNA. ABL Diagnostics therefore addresses a very wide spectrum of major indications in terms of public health.

... in an integrated continuum...

The diagnostic test kits developed, manufactured, and marketed by ABL Diagnostics (ABLD) belong to molecular diagnostics, a subset of the broader *in vitro* diagnostics (IVD) market. Molecular diagnostics, which are growing particularly rapidly, mainly focus on the identification and expression of nucleotides, the primary constituents of DNA and RNA molecules that make it possible to detect a pathogen, a biological state, a biological risk factor or the compatibility of a treatment. These PCR or sequencing kits associated with instruments and software for the interpretation of viral mutations for accredited laboratories, mainly for microbiology applications (related to HIV, SARS-CoV-2 / COVID-19, tuberculosis, viral hepatitis, etc.).
- IT dashboards and clinical database aggregation applications for research and clinical management (TherapyEdge®, Octoplus®, etc.).
- Clinical software applications for infectious disease care units, including management of the management of patients with infectious diseases (Nadis® Solution).

... thanks to molecular diagnostics...

Future cash flow or M&A target? ABL's technologies have a proven track record, generate revenue, and provide laboratory customers with cost-effective and efficient syndromic testing in a market that is looking for just that. Syndromic testing solutions are very likely to supplant conventional methods when reimbursements allow (especially in the United States). Recent history shows that large international diagnostic providers are very fond of multiplex syndromic tests and specialized PCRs, which can make ABL an obvious target, if the local market does not recognize its value.

... in important markets with unmet medical needs...

At first glance, it is important to distinguish between *the in vitro* and molecular diagnostic markets and the clinical indication markets with significant medical needs. Thus, the incidence of infectious diseases is significant and growing. While the overall *in vitro* diagnostics market has benefited from the health crisis and the Covid-19 pandemic to post significant growth rates, companies that have developed their innovation capabilities in-house are capitalizing on these new products and suffering much less from the pandemic slowdown.

... on which ABL Diagnostics represents a real opportunity.

We believe that ABL Diagnostics represents a real investment opportunity for those who want to enter the field of molecular diagnostics and therefore IVD.

2 A platform with mastered technologies

ABL Diagnostics masters a set of technologies for the detection and quantification of nucleic acids as well as the study of variations in genetic content (genotyping, sequencing), which makes it possible to obtain diagnoses of infectious diseases. Indeed, the use of molecular methods is no longer only the prerogative of specialized laboratories or reference centers but plays an increasing role in the diagnosis of common infections. The interest of these methods is especially obvious for the detection of pathogens, which are difficult to cultivate (cf. viruses, bacteria, fungi). Laboratory diagnosis of infectious diseases is currently based on two approaches:

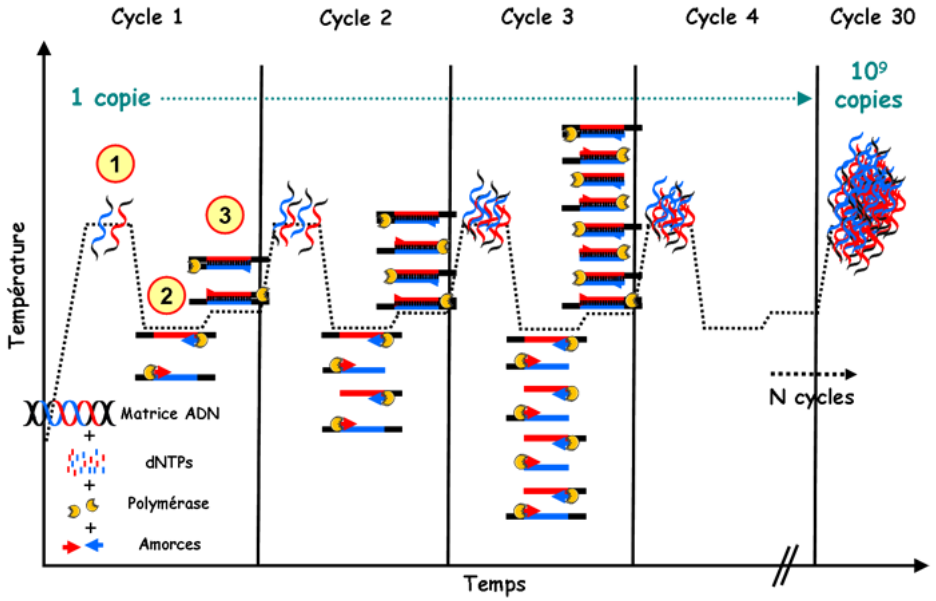
1. detect the microbe itself (directly by microscopy or after culture) or one of its molecular structures (proteins or nucleic acids);
2. measure the humoral (specific antibodies) or cellular (lymphocyte stimulation) immune response.

While DNA sequencing offers the possibility of detecting "blindly" without prior knowledge of the location of the variants sought (SNP polymorphisms, etc.), genotyping makes it possible to identify modifications at known positions, on part or all of the genome. Depending on the objective of the genotyping project, several technologies are available. These include genome-wide association studies, the Genome Wide Association Study (GWAS), as well as replication studies that require the polymorphism of several million variants spread over the entire length of the genome to be questioned on large cohorts. Very high-speed technologies (Illumina, Agilent, Affymetrix, etc.) are used for this type of project.

It is also possible to determine, with the same approach, the degree of transformation methylation (DNA methylation, histone modification) of CpG islands, which modulate biological functions. Other physical methods have been developed using MALDI-TOF or Matrix-Assisted Laser Desorption/Ionization Time of Flight technology, which is appropriate for replication/validation studies of candidate regions from a GWAS (several dozen variants) or Taqman chemistry based on allelic discrimination by amplification, used for "fine mapping" (genotyping of a few variants).

2.1 Nucleotide acid detection and quantification

The term "molecular diagnostics" refers to methods and techniques for detecting and analyzing an organism's genome, which include historical laboratory methods such as gel electrophoresis or "Southern Blotting[1]". But the advent of more recent technologies such as Polymerase Chain Reaction (PCR)[2] during the 1980s led to great advances (see the first stages of sequencing). Since then, PCR and its ability to amplify DNA and RNA has become a central and essential method in the microbiology laboratory, especially thanks to its automation.



Source: https://ed414-openlab.unistra.fr/les-tp/adn-et-genetique-2009-2012/pour-preparer-le-tp/la-pcr-quest-ce-que-cest/

According to the principle described in the diagram above, this amplification technique, alternating phases (30 to 40) of enzymatic reaction (denaturation, hybridization, and elongation) controlled by temperature steps, makes it possible to obtain up to one billion copies of the initial, complex and scarce sample. In the reaction medium, we find the initial sample of purified DNA, primers (short fragments of DNA capable of hybridizing in a specific way, on one of the two strands of DNA), the substrate in this case deoxyribonucleotides-Tri-Phosphates (dATP, dCTP, dGTP, dTTP), the heat-sensitive enzyme Taq Polymerase (which can synthesize a new strand of DNA from the template strand starting from the primer) and finally a reaction medium rich in magnesium: all of this is gathered

[1] Southern, EM. Detection of specific sequence among DNA fragments separated by gel electrophoresis. *J Mol Biol.* 1975 ; 98 :503-17
[2] Saiki, RK, et al. Enzymatic amplification of beta-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia. *Science* 1985; 230:1350–4.

in a thermal cycler (a device with a heating block, where the tubes containing our mixture for the PCR reaction are inserted and where the temperature can vary very quickly and very precisely from 0°C to 100°C). Essentially, primers are chosen to frame the sequence to be amplified, as they are the starting point of the polymerase. The trick of K. Mullis, the inventor of the method in 1983, was to use the products of each synthesis step as matrices for the following steps, without separating them from the original matrix. Thus the amplification becomes exponential, instead of linear. A few years later, he received the Nobel Prize.

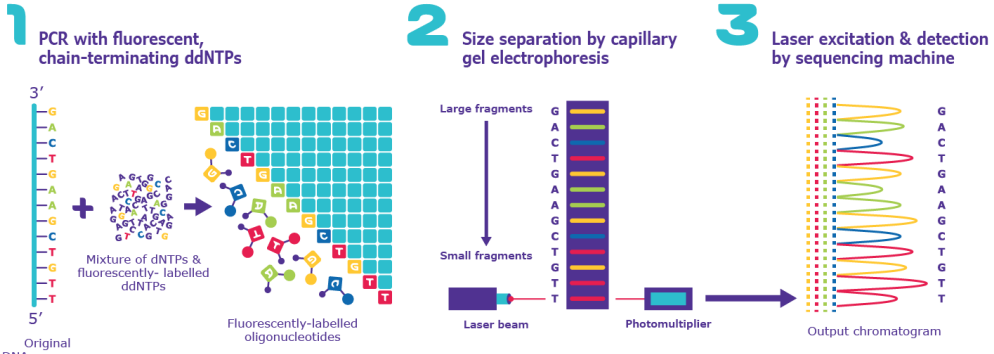
Since then, several evolutions of the core PCR technology have taken place, leading first to quantitative PCR (qPCR) and digital PCR (dPCR). qPCR is particularly useful for performing gene expression experiments, SNP detection, genotyping or allelic discrimination, as well as for validating microarray data. This technology, also known as "Real-Time PCR (RT-PCR"), consists of the detection and quantification of fluorescence whose emission is proportional to the quantity of new molecules generated during the PCR reaction[3]. In addition, this method also offers the possibility of using a wide range of fluorescent intercalators (SYBR Green) to target-specific probes (TaqMan, molecular tags, etc.). However, although the cost/sample is flexible and adapted to the criteria of the reaction (reaction volume, throughput, detection), there are limitations to the use of qPCR, especially in terms of accuracy and sensitivity for applications such as copy number variation or rare event detection.

The advent of digital PCR (dPCR), which dates back to the 80s, has long been slowed down by qPCR, but technological developments in instrumentation and chemical procedures have accelerated the development of this "limited dilution PCR". This is because in dPCR, the amplification reaction is divided into thousands of microscopic reaction volumes, is a rapidly developing alternative that is potentially more accurate[4] and precise[5]. By removing the need for a calibration curve and lower sensitivity to inhibitors due to the final fluorescence reading, dPCR is attracting more and more interest from the scientific community, particularly for studying mutations in cancer genes, monitoring the efficacy of immunotherapies, detecting pathogens, analyzing GMOs, etc. Evaluate gene editing frequencies and perform prenatal tests for genetic diseases, thus expanding its scope.

One of the most interesting advances is certainly the use of CRISPR (Clustered Regularly Interspersed Short Palindromic Repeats) technology. This genome engineering tool, which aims to produce targeted breaks in double-stranded DNA, can now be used in particular on localized sites. Indeed, it is possible to type the Mycobacterium tuberculosis complex, in particular in the context of the "spoligotyping" technique for tuberculosis, developed in 1997 by Kamerbeek et al.[6]. This genotyping technique is used to assess the diversity of CRISPR loci in the *M. tuberculosis* complex (MTBC) and remains one of the main genotyping techniques used for the molecular epidemiology of tuberculosis.

2.2 Genotyping by Sanger sequencing: the pioneering method

Genotyping has aroused a lot of interest and has contributed to the development, or even a certain form of "trivialization" of genome analysis. The aim of this method is to identify genetic modifications (mutations) at known positions on all or part of the genome. For this, several technologies are available (see above). One of the first was certainly Sanger's method. Developed in the 1970s (1977) to determine the nucleotide sequence of DNA, the Sanger method or chain termination sequencing, is the first sequencing method. It earned the Nobel Prize for its discoverer, Frederick Sanger. If at the very beginning, it was manual, Sanger sequencing was very quickly automated thanks to the emergence of sequencers. The three main steps of the Sanger method are 1) DNA sequence by chain termination, 2) Size separation by gel electrophoresis, 3) Gel analysis and sequence determination. Sanger sequencing is a molecular method that determines the unique and specific order of DNA bases by comparing the patient's sequence to a reference sequence. This technique allows the sequencing of a single gene at a time and can be performed in a targeted region or on the entire gene. The method is used to identify point mutations as well as small insertions, duplications, and deletions. The sensitivity of this method is lower than that of NGS with a detection limit of about 20% to 30%. Large deletions and duplications as well as chromosomal rearrangements are not detected by this technique.



[3] Poitras E
[4] Whale AS
Res. 2012 ; 40: e82.
[5]
ariation. *Nucleic Acids*

[6] Cowan LS, Diem L, Brake MC, Crawford JT. Transfer of a Mycobacterium tuberculosis genotyping method, Spoligotyping, from a reverse line-blot hybridization, membrane-based assay to the Luminex multianalyte profiling system. *J Clin Microbiol*. 2004 ; 42:474-477.

Source : https://www.sigmaaldrich.com/FR/fr/technical-documents/protocol/genomics/sequencing/sanger-sequencing.

1. DNA Sequence by Chain Termination

In the Sanger method, the PCR used is called chain terminated. The main difference is that oligonucleotides are dideoxyribonucleotides (ddNTPs) instead of modified nucleotides (dNTPs). While in standard PCR, DNA polymerase-catalyzed elongation could be endless as long as the reaction is fed with dNTPs, while in chain-terminated PCR, a small proportion of ddNTPs are present with conventional dNTPs and when DNA polymerase randomly incorporates a ddNTP, the elongation stops, because ddNTPs do not possess the 3'-OH group necessary for the formation of a phosphodiester bond. A chain-terminated PCR produces millions or even billions of copies of oligonucleotides of the DNA sequence of interest terminated, after a random length (n), by 5'-ddNTPs. In manual Sanger sequencing, four PCR reactions are set up, each receiving only one type of ddNTP (ddATP, ddTTP, ddGTP, or ddCTP). In automated Sanger sequencing, all ddNTPs are mixed in a single reaction, and each of the four dNTPs has a unique fluorescent label.

2. Size separation by gel electrophoresis

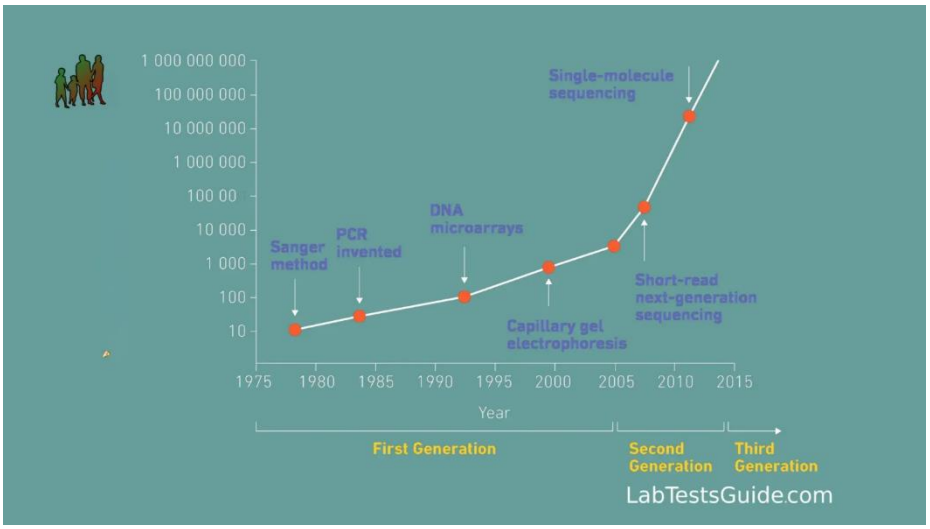
Then, oligonucleotides with different chain lengths are separated according to their size by gel electrophoresis. In gel electrophoresis, DNA samples are deposited at one end of a gel matrix and an electric current is applied; As the DNA is negatively charged, the oligonucleotides are attracted to the positive electrode at the other end of the gel. Since all DNA fragments have the same charge per unit mass, the speed at which oligonucleotides move is determined solely by their size. The smaller a fragment, the less friction it undergoes as it moves through the gel, and the faster its migration speed, the farther it will go over the gel. Thus, the oligonucleotides are arranged from smallest to largest when the gel is read from bottom to top. In manual Sanger sequencing, oligonucleotides from each of the four PCR reactions are deposited on four different tracks of a gel. This makes it possible to identify the oligonucleotides corresponding to each ddNTP. In automated Sanger sequencing, all oligonucleotides are analyzed in a single capillary gel electrophoresis in the sequencer.

3. Freeze analysis and sequence determination

The final step is simply to read the gel to identify the starting DNA sequence. Since DNA polymerase synthesizes DNA only in the 5'→3' direction from a supplied primer, each terminal ddNTP corresponds to a specific nucleotide in the starting sequence (e.g., the shortest fragment must end at the first nucleotide from the 5' end, the second shortest fragment at the second nucleotide from the 5' end, and so on). By reading the gel from the smallest to the largest strip, it is therefore possible to determine the 5'→3' sequence of the original DNA strand. In manual mode, the user simultaneously plays the four tracks of the freeze from bottom to top, using the track to identify the terminal ddNTP of each band. For example, if the bottom band is in the column corresponding to the ddGTP, it means that the smallest fragment of PCR ends in a ddGTP, and thus, that the first nucleotide from the 5' end of the starting sequence contains a guanine base (G). In automated mode, a computer reads each band of the capillary in order, using fluorescence to determine the identity of each terminal ddNTP. In a few words, a laser excites the fluorescent markers in each band and a computer detects the emitted light. Because each of the four ddNTPs has a different fluorescent marker, the light emitted can be directly associated with the identity of the terminal ddNTP. The result obtained is a chromatogram showing the fluorescence peak of each nucleotide along the template DNA.

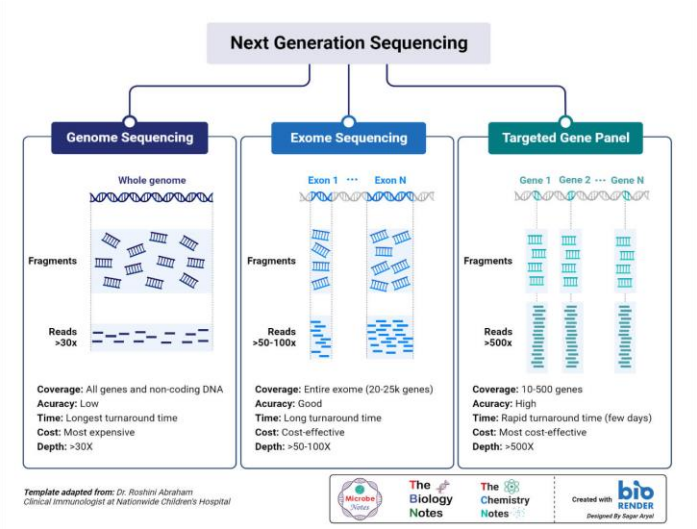
2.3 Next Generation Sequencing (NGS)

High-throughput or Next Generation (NGS) sequencing is a molecular methodology that allows the rapid sequencing of large amounts of DNA or RNA (from thousands to millions) simultaneously by determining the unique and specific order of nucleic acid bases. This tool therefore allows the sequencing of several genes and several individuals simultaneously, by comparing the patient's sequence to a reference sequence. It is the result of the convergence of technologies, which has enabled the emergence of new types of machines capable of performing several million sequence reactions in parallel, then analyzing the results and processing the information obtained. These automatons are called very high-throughput sequencers or next-generation sequencers. With the emergence of these new massive sequencing technologies, often grouped under the acronym NGS for *Next Generation Sequencing*, capacities have been exponential. Today, a single machine can sequence 1 Terabase (Tb) in less than a day, and the technological developments announced are even more dizzying. Initially, the throughput of manual analyses was about 5 days for 800 base pairs (bp) and required the use of radioactive nucleotides.



Source : https://www.labtestsguide.com/next-generation-sequencing-ngs

One of the greatest scientific advances of the last few decades was without context the publication of the sequence of the human genome in 2001[7]. Despite its incompleteness at the time of publication, the sequencing technologies put in place to achieve this performance have continued to develop, making it possible to move from slow and laborious methods to ever faster technologies. With the development of automatic capillary sequencers, a convergence has taken place between three fields that were previously compartmentalized: microfluidic techniques (circulation of liquids in capillaries of the order of a micrometer in size), nanotechnologies (possibility of manufacturing objects the size of a billionth of a meter), and finally advances in computer science, which follow Moore's law (doubling of information processing capacities every 18 months).



Source : https://microbenotes.com/next-generation-sequencing-ngs/#pyrosequencing

These techniques have allowed a real acceleration of the sequencing procedure as can be seen in the figure above. This acceleration is not only in time (faster completion of the process) but also in terms of the number of sequenced databases, since in about ten years, capacities have increased from a hundred databases to more than 10 million databases. The aim was to reduce the cost of sequencing genetic material beyond what is possible with previous methods (mainly Sanger).

NGS have overcome the limitations of conventional DNA sequencing methods and have been used in a wide range of molecular biology applications. With these recent and still evolving technologies, we can understand a variety of genetic fragments that are increasingly important in terms of size, from global "Whole Genome Sequencing" to specific genes and WES "Whole Exome Sequencing". It is certainly this multiplicity of approaches that is one of the strengths of the SNE. There are several generations of SNGs:

- First generation: "Sanger" capillary sequencing.
- Second generation: pyrosequencing, reversible terminal chemistry sequencing, ligation sequencing;
- Third generation: single-molecule fluorescent sequencing, real-time single-molecule sequencing, semiconductor sequencing, nanopore sequencing.
- Fourth generation: genomic analysis directly in the cell.

[7] (Lander ES et al., 2001)

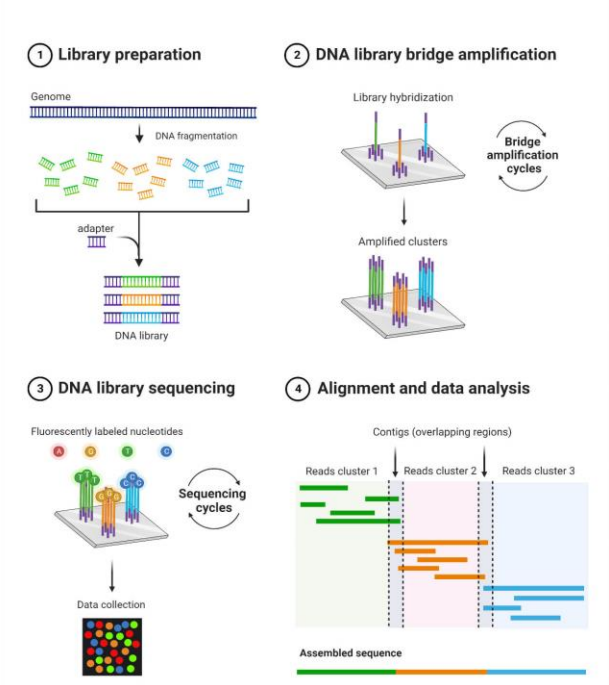
We are still in the second generation of SNGs, which continues to develop around three main sequencing strategies:

- One with a short read on paired sequences of 150 bp (base pairs) with low error rates (0.1 to 0.5%), mainly the Illumina technology (Solexa);
- Another with a longer read, between 10 and 100 kb (i.e. between 10,000 and 100,000 bp) on single monomolecules, developed by Pacific Biosciences or Oxford Nanopore Technologies, however, the error rates are higher (10 to 15%);
- A so-called linked readout, using 10X Genomics' technology, which generates short Illumina reads encoded from longer molecules (for example, 50 kb), a sort of mix between the Illumina-type short read and tags.

However, for reasons of cost, ease of use and accuracy, the Illumina method is now the most widely used method in the world for genomics studies by NSE. In addition, the SNG offers the possibility of working on both DNA and RNA. On DNA, the method is used to identify point mutations as well as small insertions, duplications, and deletions. NGS is particularly useful when several genes of interest need to be tested, which is the case in myeloid hematologic malignancies. The method shows a high sensitivity with a detection limit of 5% for hotspot mutations and 10% for other mutations at diagnosis. In a follow-up context, a lower detection limit may be applied (up to 1-2%). However, the method is not quantitative and does not allow the detection of large changes. The RNA method is used to identify fusion genes obtained when a sequence is fused with other sequences of the same or a different gene. However, the method is not quantitative.

2.3.1 Illumina's Method

Developed by Solexa, this sequencing technology based on dye terminators. In this method, it is necessary, during the preparation phase, to obtain small fragments of DNA, in particular by denaturing it in order to obtain optimal fragmentation.



Source : https://microbenotes.com/next-generation-sequencing-ngs/#next-generation-sequencing-types

Then these fragments are ligated in some places by small oligonucleotides (6 to 8 bases). These adapters are used twice as much for the construction of the library with each sample as its own pair of adapters and for hybridization on the Illumina® flowcell via a small complementary sequence. After this stage, where the DNA molecules are first attached to this carrier and amplified by PCR. This is called bridge amplification. Unlike pyrosequencing, DNA can only be extended by one nucleotide at a time.
The denaturation-amplification-washing cycle is repeated many times with the synthesized "clone", which will remain fixed on the slide (flowcell) while the second "original" part will not be fixed will be washed out of the plate. This whole procedure will be repeated many times, this is the cluster generation or "clustering" step. At the end of the process, only the direction strands remain on the slide and sequencing can begin after a primer has been attached to the oligonucleotides. Sequencing is performed with a polymerase and specific nucleotides labeled with a fluorochrome and possessing a chain terminator effect. It is the unfolding of a cycle that will be repeated for each base. These nucleotides are then excited by a laser that will emit a fluorescent signal and will be captured and integrated into the computer. For a cluster, all identical strands will read at the same time. For each sample, we will have thousands of reads This number of reads indicates the depth of the sequencing. The more readings we have, the more sensitive the sequencing will be.

2.3.2 La technologie Ion torrent® : Life technologies (Thermo Fisher Scientific)

Introduced in the 2010s, Ion Torrent sequencing corresponds to a higher level of convergence and integration of technologies than previous methods. It sought to respond to other problems such as detection that is neither radioactive nor luminous, the simplest being to detect the synthesis directly, via a transistor sensor, without using labeled nucleotides. It is therefore a sequencing by synthesis and a detection of chemical changes during the synthesis reaction by an electrochemical method. If clonal amplification is also performed during emulsion PCR using ionic spherical particles, the major differentiation is in the detection method. This is because the sequencing matrix is loaded onto an Ion Torrent chip made up of semiconductor circuits at the bottom of each well. During the synthesis of polynucleotides, as in other methods, the release of pyrophosphate by the incorporated nucleotide is observed, detectable by the ad-hoc detector. Then, the release of a hydrogen ion of the 3' OH group from the incorporation site on the growing strand would lead to a change in the pH of the medium, which is also detectable. Thus, during each polymerization of nucleotides, it will be possible to detect the incorporation of the nucleotide, either by the emission of pyrophosphate or the change in pH. Transistor detection of H+ is a more established technology (cf. the widely used solid-state pH meters). While this technique is fast and offers good value for money, it is still relatively little used because of difficulties in sequencing homopolymers and the weakness of bioinformatics tools.

2.3.3 3rd generation NGS

The principle of the third generation NGS corresponds to the sequencing of a DNA molecule without a pre-amplification step, unlike the first and second generation technologies (type 454 Roche and Life Technologies, Ion Proton from PGM Ion Torrent, HiSeq™ from Illumina). However, these methods retain the incorporation of nucleotides, in a cyclic manner. Single Molecule Sequencing or SMS technologies are grouped into three categories:

- Real-time sequencing technology involving the synthesis of the complementary DNA strand via DNA polymerase.
- Sequencing techniques by successive basic detection of a DNA molecule through nanopores.
- Sequencing technologies based on microscopy techniques.

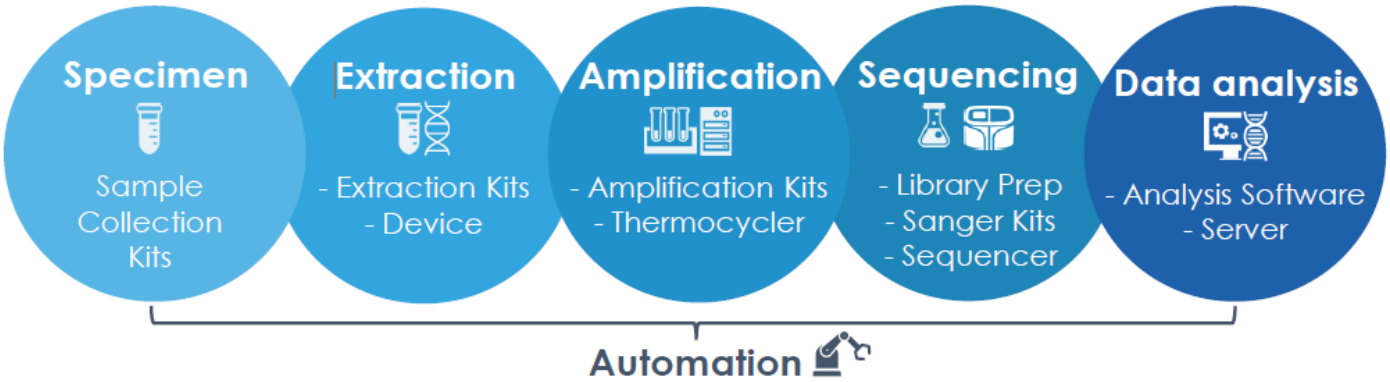
The contribution of the latest nanofabrication, surface chemistry and optics techniques has enabled Pacific Biosciences to design and develop a new SMRT "Single Molecule Real Time Sequencing" platform. A method that can be found at Helicos Biosciences under the name "tSMS" for "true Single Molecule Sequencing", although its cost and the need for shutdown cycles could link it to the second generation.

3 A range of products for infectious diseases

ABL Diagnostics has developed a range of products for the routine detection of a number of viruses inducing serious and disabling chronic infectious diseases. Indeed, thanks to its technologies, ABL masters the major techniques allowing both the detection and identification of the main viruses and bacteria, but also the company can determine and monitor their mutations, responsible for escape phenomena or therapeutic resistance. ABL has therefore implemented a complete solution for genotyping in microbiology.

3.1 DeepChek®, the central platform

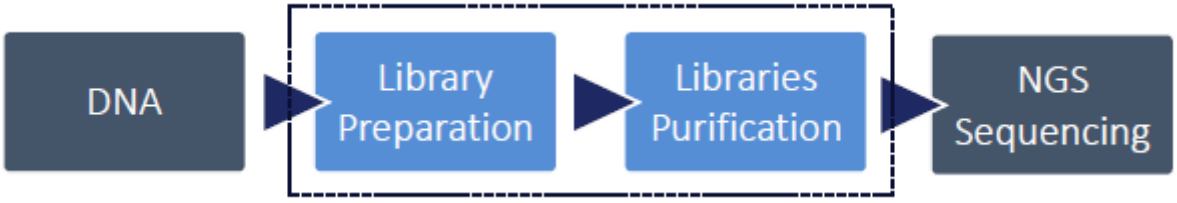
DeepChek® is therefore the complete genotyping solution developed by ABL, which can be broadly divided into five main steps from sample collection to data analysis, oligonucleotide material extraction, sample amplification and sequencing.



Source: Corporate presentation of the company

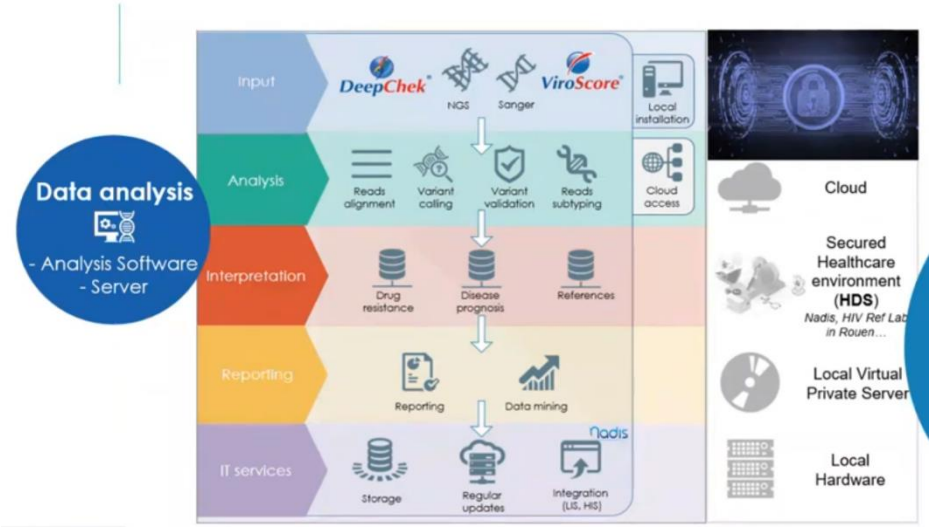
This entire workflow can be automated, from the use of pipetting robots to the extraction of nucleic acid molecules (RNA, DNA), the amplification of primers and tags, the sequencing of course as well as the analysis of the raw and improved data produced.

1. Sample collection is an essential step in the process, as it is necessary to adapt the collection tool to the pathogen's location environment. The types of biological samples are therefore multiple (serum, plasma, blood, sputum).
2. The extraction of biological material can be carried out either manually or automatically initially from the sampling tool, then for cell lysis and the recovery, if possible, with a high yield, of the oligonucleotide material (RNA or DNA) in an acceptable way for the further process.
3. The amplification part is mainly carried out by PCR, which is the simplest way to increase the genomic material. In addition, this amplification will have to be adapted to the next stage of sequencing (Sanger, SNG, etc.) as well as to the volume of tests to be carried out.
4. The sequencing offered by ABL can be carried out in two distinct ways. The first is the Sanger method for which the company has developed its own reagent kits that can be used on multiple machines or platforms. ABL has set up an integrated process for the second technique, that of SNG, which results in the rapid construction of libraries, thanks in particular to a complete kit for the preparation of libraries by enzymatic route in input quantities (100 pg - 500 ng) adapted to all Illumina platforms and which will be applied to other platforms (MGI, NanoPore, Ion Torrent). Compatible with the genomes of different species



Source: Corporate presentation of the company

5. Data analysis through proprietary DeepChek®, MicrobioChek™ and ViroScore® software. This software, developed in Web technology with Cloud access and HDS (Health Data Hosting) hosting, makes it possible to produce a genotyping report generated by virologists for clinicians based on raw sequencing data. This analysis procedure, which will use the raw data stored in the . FASTQ for NGS or chromatograms generated by the Sanger method, align the sequences (reads), determine variants with their mutations (SNPs) and then validate them and subtype. A set of information is stored, before being interpreted clinically (resistance, prognosis, vaccine escape, etc.) and compared to references, thanks in particular to the series of integrated algorithms that are continuously updated (Stanford, ANRS, etc.) according to the type of analysis.

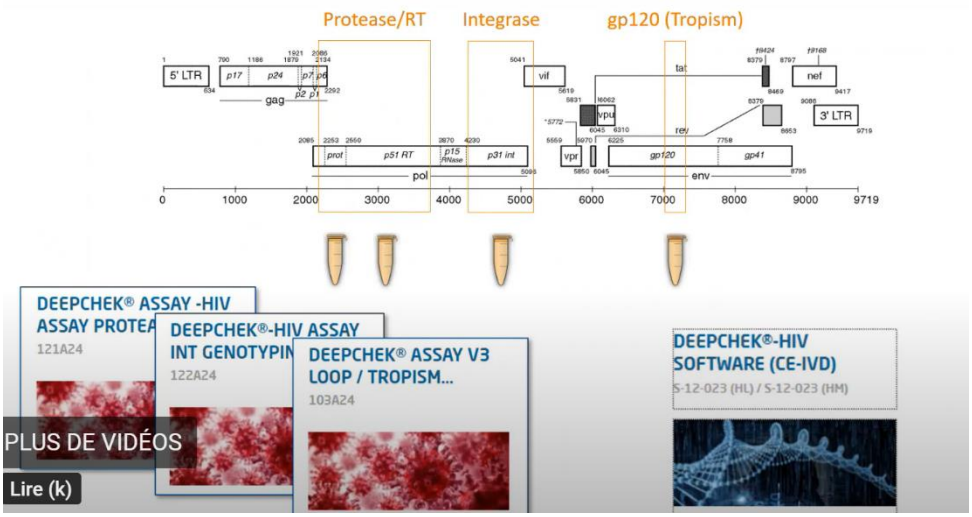


Source : Présentation Corporate de la société

Data exploitation is carried out in the form of reports in different formats for clinicians, or for research or publications. In addition, the complete platform (DeepChek®, MicrobioChek™ and/or ViroScore®) can be integrated into the user's local network (SIL or HIS) or into the NADIS® clinical data processing software developed and marketed by ABL Diagnostics (feedback of information relating to virology or bacteriology in the patient file). This software component also makes it possible to retain virologists and to appropriate the tool in the long term. ABL also offers various services, including the import of historical data into the database integrated into the various software, which makes it possible to optimize customer satisfaction and target an efficient transition from any third-party software or methodology.

3.2 DeepChek® HIV, the initial approach

ABL's diagnostic kits for Human Immunodeficiency Virus (HIV) come in three distinct approaches that correspond to the natural history of HIV-1 infection. This is influenced by the genomic organization of the virus, its genetic diversity and its replicative cycle. First of all, a few words about HIV. HIV-1, which was isolated in 1983 by the team of Professors Barré-Sinoussi and Montagnier, [8] is the pathogen of acquired immunodeficiency syndrome (AIDS). HIV-2 was discovered three years later by Prof. Clavel's team[9]. They both belong to the *Retroviridae family* and the Lentivirus genus. Viruses characterized by the presence of reverse transcriptase (TI) which allows the retro-transcription of their genome in RNA form into single-stranded DNA. Despite having the same genomic organization and structure, the genetic proximity between HIV-1 and HIV-2 is only 49%.[10] In fact, their proteins have different molecular weights, as well as the natural history of infection is also different. This 9.6-kilobase RNA molecule has two non-coding regions with repeated sequences (long terminal repeat or LTR) at its ends, which are involved in the integration of the virus and its transcription. There are also three structural genes: *gag, pol, env*.



Source : Lugehetmann & Heim Webinar Presentation Session II

- *Gag* codes for structural proteins such as matrix (p17), capsid (p24) and nucleocapsid (p6-p7) proteins.
- *Pol* codes for protease (p12), retro-transcriptase (p51 and p66) and integrase (p32).
- *ENP* code for envelope glycoproteins (GP120 and GP41).

There is also a whole series of genes that participate in the regulation of the virus's machinery, complicating its genetic organization, such as the *tat* genes for *transactivator of transcription* and *rev* (*regulator of viral expression*), which participate in the regulation of transcription. The *viral infectivity factor (vif), negative expression factor (nef), viral protein r (vpr)* and *viral protein u (vpu)* genes encode accessory proteins that are essential for the *in vivo replication* of the virus[11].

In the figure above, ABL has therefore developed five main diagnostic kits and specific software:

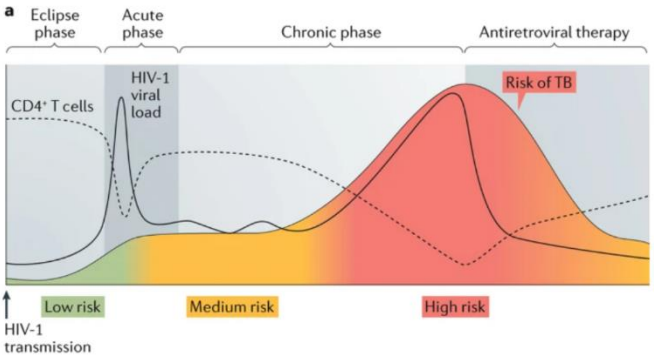
- DeepChek® Assay PROTEASE / REVERSE TRANSCRIPTASE Genotyping and Drug Resistance V1 and DeepChek® Assay INTEGRASE Genotyping and Drug Resistance V1 mainly target the interaction genes (protease, RT, and integrase) that allow the viral genome to reproduce and integrate into the genome of human lymphocytes. Indeed, HIV-1 RT has three distinct enzymatic functions:
  - a DNA-dependent RNA-dependent polymerase function transforming genomic RNA into single-stranded DNA.
  - RNAse activity for the destruction of RNA that served as a model.
  - another DNA-dependent DNA polymerase activity to synthesize double-stranded DNA (which eventually integrates into the chromosomal DNA of the infected cell through viral integrase[12].
- DeepChek® Assay HIV-1 Full PR/RT/INT Drug Resistance, an optimized version targeting the three main resistance genes (protease, reverse transcriptase, and integrase) in a single PCR reaction, ensuring simplified use of the methodology and accessibility to all virology laboratories.
- DeepChek® Assay HIV Tropism which targets the crucial interaction between the human CD4 receptor and viral gp120 for the entry of the virus into the T cell or any antigen-presenting cell (monocytes, dendritic cells, Langerhans cells or microglia).
- DeepChek® Assay Whole Genome HIV-1 Genotyping, which is the only in vitro diagnostic solution to genotype the HIV-1 virus through whole genome sequencing.
- DeepChek® HIV Software

[8] Barré-Sinoussi F. et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Sci* 1983 ; (220):868–71.
[9] Clavel F. et al. Isolation of a new human retrovirus from West African patients with AIDS. *Sci* 1986 ; (233):343–6.
[10] Peeters M, Mulanga-Kabeya C, Delaporte Ć. The genetic diversity of HIV1. *Virology*. 2000 Oct.; 20; 4(5):371–81.
[11] Charpentier C, Damond F, Brun-Vézinet F, Descamps D. Human immunodeficiency virus. *EMC - Mal Foul.* 2011 Jan; 8(4):1–12.
[12] Engelman A, et al. The structural biology of HIV-1: mechanistic and therapeutic insights. *Nat Rev Microbiol.* 2012 Mar ; 16; 10(4):279–90.

3.3 DeepChek® and the resurgence of tuberculosis

For several years, there has been an upsurge in infections and active forms of tuberculosis. Due to its presence in the general population and the phenomena of co-infection with *Mycobacterium tuberculosis*, tuberculosis has become the leading cause of death among people infected with HIV-1. Multiple scientific studies have shown that HIV-1 infection modifies the course of *M. tuberculosis* infection and significantly increases the risk of active tuberculosis. It is also clear that tuberculosis increases the levels of replication, spread and genetic diversity of HIV-1. Therefore, co-infection has reciprocal benefits for both pathogens. Indeed, while HIV-1 infects CD4+ T cells and macrophages, while *Mycobacterium tuberculosis* mainly affects macrophages, which need CD4+ T cells to increase the intracellular elimination of microbial pathogens. It is therefore thought that the depletion of CD4+ T cells associated with HIV-1 infection plays a major role in the increased risk of tuberculosis in HIV-1-infected individuals.

Thus, the risk of tuberculosis is multiplied by 2 to 5 in the event of early infection with HIV-1 and by more than 20 in the event of advanced HIV-1 infection. Despite antiretroviral therapy (ART), the risk of tuberculosis remains high (x4 approximately) in HIV-1 infected patients.



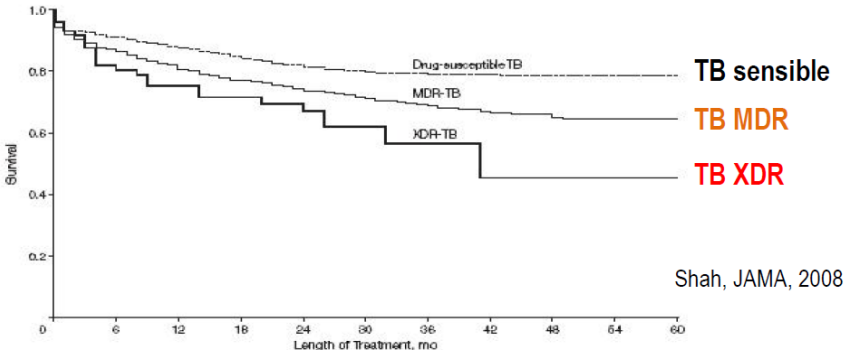
Source : Nature Reviews Microbiology,

The course of HIV-1 and tuberculosis is characterized by chronic inflammation due to the inability to eliminate either pathogen. The chronic nature of these responses may compromise host protection by promoting an immunoregulatory phenotype characterized by attenuated T cell responses.
Advanced HIV-1 infection is associated with reduced immunopathology of TB co-infection, but the introduction of antiretroviral therapy can exacerbate the immunopathology of TB, giving rise to immune reconstitution inflammatory syndrome (IRIS). This syndrome reflects the recovery of inflammatory innate immune responses to *M. tuberculosis*, which may be exacerbated by the recirculation of M. tuberculosis-reactive T cells and the failure of normal homeostatic control of inflammatory responses. The pro-inflammatory response to *M. tuberculosis* may exacerbate the progression of HIV-1/AIDS disease by increasing the spread of the virus through increased transcription and cell-to-cell transmission. An estimated two billion people, or a quarter of the world's population, have been infected with tuberculosis[13]. Within this complex, the two major contributors are *Mycobacterium tuberculosis* (*M. tuberculosis*) and *Mycobacterium bovis* (*M. bovis*). *M. tuberculosis* is the leading cause of tuberculosis in humans and is transmitted through aerosols that an infected person emits when coughing, sneezing, spitting, or even [14]talking. *M. bovis* is responsible for bovine tuberculosis and has the largest number of guests within the complex, including its main one, cattle. The spread of these mycobacterium is mainly respiratory, however, the ingestion of infected food and water can also lead to infection[15]. *M. bovis*, being also capable of causing tuberculosis in humans, which is known as a neglected zoonosis. It is therefore essential to detect and diagnose it in human populations. The identification of MTC species is currently based on a few phenotypic traits and the detection of species-specific polymorphisms in certain genes.

The use of advanced molecular techniques such as mycobacteria-intersected repeating units analysis - variable-number tandem repeats (MIRU-VNTR), spacer oligonucleotide typing (Spoligotyping), restriction fragment length polymorphism (RFLP) analysis, and next-generation sequencing (NGS) for strain typing allows TB progression to be tracked, compare the profiles of various isolates[16]. However, combined with the resurgence of infections, there is an increase in the prevalence of drug-resistant tuberculosis. Among the observations, we note that only 6 out of 10 anti-tuberculosis treatments using first-line drugs have succeeded in curing the infection in European countries. If properly planned and carried out, TB treatment should be successful in about 9 out of 10 patients infected with strains that respond to the antibiotics rifampicin and isoniazid. In addition, only 48% of patients with both TB and HIV in the Region and 54% in the EU/EEA who started TB treatment in 2021 had been cured.

[13] Behr MA, et al. Latent tuberculosis: Two centuries of confusion. *Am. J. Respir. Crit. Care Med.* 2021;204(2):142–148.
[14] Kaufmann SH, Schaible UE. 100th anniversary of Robert Koch's Nobel Prize for the discovery of the tubercle bacillus. *Trends Microbiol.* 2005;13(10):469–475. doi: 10.1016/j.tim.2005.08.003.
[15] Jenkins AO, et al. Molecular epidemiology of human and animal tuberculosis in Ibadan, Southwestern Nigeria. *Vet. Microbiol.* 2011;151(1):139–147. doi: 10.1016/j.vetmic.2011.02.037.
[16] Tornheim JA, et al. Building the framework for standardized clinical laboratory reporting of next-generation sequencing data for resistance-associated mutations in *Mycobacterium tuberculosis* complex. *Clin. Infect. Dis.* 2019; 69:1631–1633.

Multidrug resistance (MDR) of Mycobacterium tuberculosis to antibiotics is defined by simultaneous resistance to at least: – *isoniazid* – *rifampicin*. Ultradrug resistance (XDR) is defined by resistance to isoniazid and rifampicin as well as – fluoroquinolones – one of the reserve aminoglycosides (*amikacin, kanamycin, capreomycin*).



Source : Shah, JAMA 2008

3.4 DeepChek® and the alphabet of liver viruses (HCV, HBV, HDV)

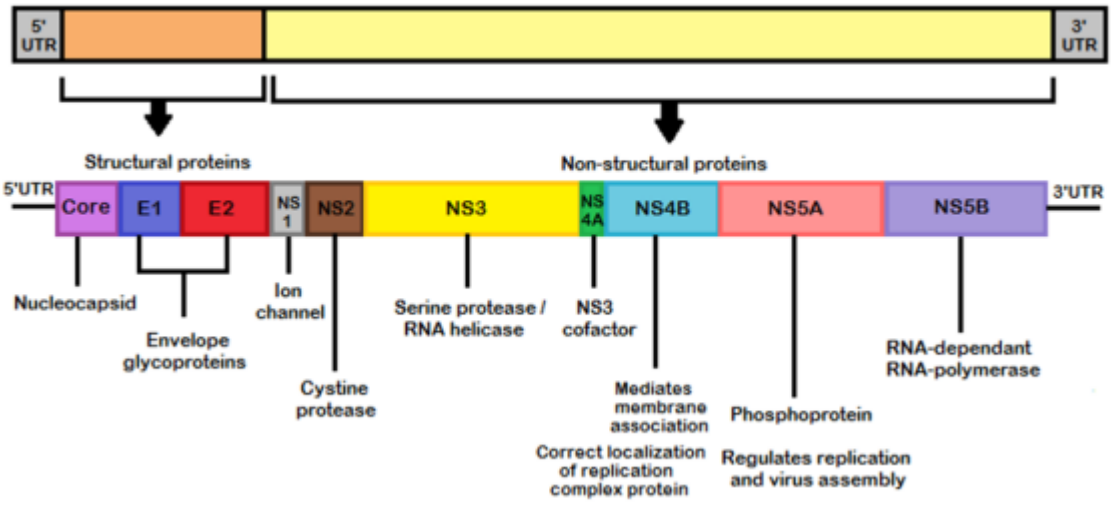
Building on the expertise developed in HIV, ABL Diagnostics has taken an interest in the viruses responsible for viral hepatitis. Indeed, these diseases in the growth phase throughout the world are characterized by viruses with multiple genotypes, as well as co-infection phenomena for some of them (HBV-HDV), requiring ever more accurate and early diagnosis. In addition, the advent of new antiviral molecules, after sofosbuvir in 2012, requires a good understanding of virus genotypes.

3.4.1 HCV

HCV belongs to the *Flaviviridae or Flavivirus* family, a family of RNA viruses that mainly infect mammals and includes yellow fever, West Nile, dengue fever and Zika. HCV, which is constantly evolving molecularly, has multiple genotypes (about 7) which must therefore be characterized before any relevant therapeutic procedure is taken. A quick reminder about the genomic organization of HCV, which is presented as a simple strand of RNA with a linear open reader frame flanked at each end by a non-coding region. During transcription, RNA gives a single giant polypeptide precursor which is then cleaved by cellular proteases for the core, E1, E2 parts (envelope structure proteins)[17] and by viral proteases for the non-structural part (NS1, NS2, NS3, NS4A, NS4B, NS5A, NS5B).

The significant genetic variability in HCV is related to:

- A viral RNA polymerase that makes mistakes without the ability to correct them, leading to an accumulation of mutations on the genome during replication.
- Selection pressures exerted in particular by the host's immune responses.
- Constraints on the genome linked to the need to preserve the structures and genomic and protein functions vital to the virus.



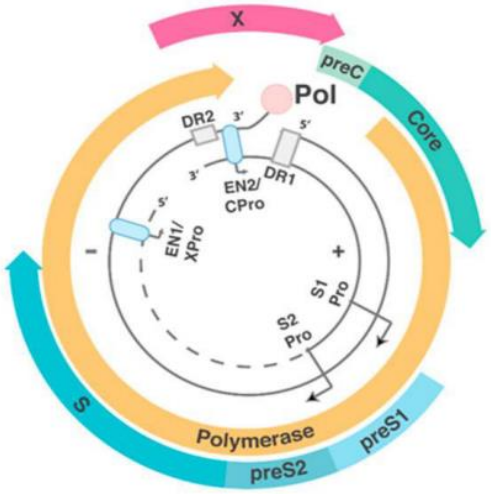
Source : Amin et al. Malaysian Journal of Medicine and Health Sciences (2023) 19(5):359-370.

[17] Les virus des hépatites [Internet]. [cited 2019 Aug 15]. Available from: http://www.microbesedu.org/etudiant/hepatites.html

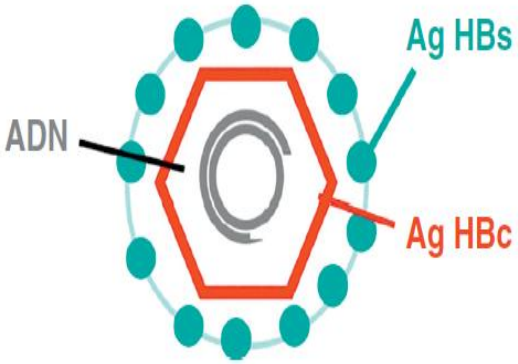
Recent data suggest seven different genotypes for HCV with a genomic divergence of about 30 to 35% and several subtypes with nucleotide sequences varying from 20 to 25% between two subtypes[18]. Thus, in France, HCV genotype 1 (1a and 1b) is the most common (61%), followed by genotype 3 (19%), genotypes 2 (9%), 4 (9%), 5 (2%) and 6 (< 1%) are rarer. Type C viral hepatitis is the most common, along with type B hepatitis, followed by type A, type D and finally type E hepatitis. Viruses A and E are frequently present in the feces of infected people, often with oral contamination (water, food, soiled hands) in areas where hygiene, sewage disposal or disinfection practices leave much to be desired.

3.4.2 HBV

The Hepatitis B Virus (HBV) is also characterized by a strong genetic polymorphism, which influences the natural course of the disease and the phenomena of therapeutic resistance often associated. This virus of the *Hepadnaviridae* family, whose infective particle is spherical in shape with a diameter of 42-47 nm, represents a real public health problem at the global level[19], since in 2016, nearly two billion people were infected with HBV, including 400 million chronic[20] carriers. This enveloped virus contains a DNA molecule inside a capsid, the genomic organization of which is described in the figure below. The four open reading frames (ORFs) represented here by different colors allow the synthesis of 7 proteins. They are delimited in green for genes relating to the structure of the capsid of the virus (Prev, core) encoding the proteins of the capsid or HBc antigen (HBcAg) and the HBe protein (HBeAg) secreted into the bloodstream. In blue, the S frame with the genes (preS1, preS2 and S) which encodes the 3 envelope proteins: L (*large*), M (*medium*) and S (*small*) as well as for the HBs antigen (HBsAg). The P (yellow) frame, which represents 80% of the HBV viral genome, encodes DNA polymerase, which is responsible for the replication of the virus. In addition, DNA polymerase also has reverse transcriptase (TR) and RNase activity. The last reading frame in red X encodes the X protein or HBx antigen (HBxAg). There are also a number of cellular proteins (kinase, heat shock).



Source : https://www.sfm-microbiologie.org/wp-content/uploads/2019/02/VIRUS_HEPATITE-B.pdf



Source : Structure de la particule virale https://aemip.fr/?page_id=3750

The variability of HBV was initially highlighted according to the antigenic properties of the different antigens, in particular HBsAg (envelope protein). This allowed a first classification based on the serological characteristics (serotypes) of HBsAg and other antigens (HBeAg, HBcAg, HBxAg). But with the advancement of technology and sequencing, the monitoring of variability has shifted to the study of whole genomes. Also, multiple scientific teams have studied the genetic polymorphism of HBV, in order to understand the viral factors influencing the evolution of the disease.

Recent work has shown that there are ten different genotypes around the world, designated by letters from A to J and distributed according to different geographical areas[21] as can be seen in the following figure, which shows the genotypes as well as their subtypes and their representation within a sample of the Asian population. In addition, it is known that genotypes influence the course of the disease and the effectiveness of treatment[22].

[18] Fougerou-Leurent C, Thibault V, Bellissant E. Mechanisms of action of DAAs for the treatment of hepatitis C. *The Pharmacologist's Letter*, 2016, Vol. 30, p.6-7.
[19] Kao JH, Chen DS. Global control of hepatitis B virus infection. *The Lancet Infectious Diseases.* 2002; 2(7):395–403.
[20] De Franchis R, et al. EASL international consensus conference on hepatitis B. 13-14 September 2002 Geneva, Switzerland. Consensus statement (long version) *J Hepatol.* 2003;39(Suppl 1):S3–25.
[21] Liu CJ, Kao JH. Global perspective on the natural history of chronic hepatitis B: role of hepatitis B virus genotypes A to J. *Semin Liver Dis.* 2013;33(2):97–102.
[22] Wagner A, et al. Hepatitis B virus genotypes. *Immuno-analysis & Specialized Biology.* 2004;19(6):330–342.

Genotype	Subtype	Geographic location
A	A1	Sub-Saharan Africa
	A2	Northern Europe
	A3	Western Africa
B	B1	Japan
	B2-B5	Taiwan, China, Indonesia, Vietnam, Philippines
	B6	Alaska, Northern Canada, Greenland
C	C1-C3	Taiwan, China, Japan, Korea, Southeast Asia
	C4	Australia
	C5	Philippines, Vietnam
D	D1-D5	Africa, Europe, Mediterranean basin, India
E		Restricted to West Africa
F	F1-F4	Central and South America
G		France, Germany, United States
H		Central America
I		Laos, Vietnam
J		Japan

	Prevalence (%) of HBV genotype				
Country	A	B	C	D	Others
China	2	41	53	1	1
Hong Kong	0	33	63	0	4
Japan	2	12	85	0	1
Korea	0	0	100	0	0
Philippines	51	22	27	0	0
Solomon	0	0	55	45	0
Taiwan	3	71	22	0	4
Thailand	1	12	87	0	0
Vietnam	22	12	30	24	12

Source : Kao, JH - Molecular Epidemiology of Hepatitis B Virus ; Kor. J Int Med. 2011.

3.4.3 VHD

Identified in 1977 by Rizetto and his team[23], in liver biopsies, the hepatitis D virus is a defective RNA virus. Initially discovered in patients with chronic hepatitis B, the teams showed that HDV replication requires the presence of hepatitis B surface antigen HBs (HBsAg). A situation that explains the co-infection phenomena often observed. With an RNA genome of only 1.68 kb, it would be the smallest known genome of mammalian viruses[24]. It replicates via a complementary intermediate RNA (anti-genome) as well as a messenger RNA. In the HDV replication cycle within the infected liver cell, genomic RNA is replicated into anti-genomic RNA that complements genomic RNA and encodes HD antigen (AgHD).[25] There is another region called "viroid-like" that can be found on both genomic viral RNA and anti-genomic RNA that encodes an autolytic ribozyme activity involved in viral replication. Initially classified into three genotypes, HDV genotyping has recently benefited from scientific advances, which have made it evolve into a greater number of classes, each linked to a different geographical and clinical distribution, All these genotypes (eight) that have been characterized have a great variability of sequence, up to 35% difference, a potential indication of a different origin depending on the genotypes. Genotype 1 associated with viral infections is considered ubiquitous[26]. Genotype 2, mainly found in East Asia (Japan, Taiwan and Russia),[27] is of moderate pathogenesis as is genotype 4 (IIb), which is also restricted to Japan and Taiwan. Genotype 3 observed in South America is considered to be the most aggressive genotype and induces severe fulminant hepatitis in patients[28]. Finally, genotypes 5 to 8 have been isolated in Africa[29]. Interestingly, it has been shown that certain HDV genotypes are more easily associated with a particular HBV genotype.

3.5 DeepChek® and ubiquitous viruses (CMV, HSV, HHV, EBV)

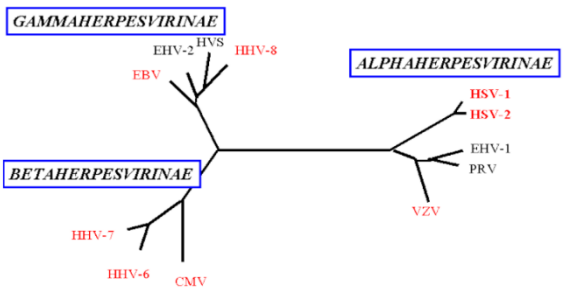
Human *Herpesviridae*, including cytomegalovirus (CMV), herpes simplex, Epstein-Barr virus and varicella-zoster virus, is a family of DNA viruses characterized by a high persistence (many years), latently, in the body after primary infection. The reservoirs of these viruses are blood or nerve cells. The natural history of these infections is often marked by endogenous reinfections or symptomatic or non-symptomatic reactivations, the most frequent and most serious of which affect subjects with an immune deficiency (of T cells following transplantation or HIV infection).

The *Herpesviridae* family, which has more than a hundred species, is divided into three subfamilies:

- *Alphaherpesvirinae,* which includes the genera Simplexviruses (HSV-1 and -2) responsible for herpes and Varicellovirus (VZV) responsible for chickenpox and shingles; these viruses infect epithelial cells and can remain latent in the sensory nerve ganglia,
- *Betaherpesvirinae* with the genera Cytomegalovirus (HCMV) and Roseolovirus (HHV-6), responsible for sudden exanthema (infantile roseola); these viruses are often responsible for asymptomatic infections that can remain in a latent state in the blood, lymphoid tissue, secretory glands and kidney.

[23] Rizzetto M, *et al*. Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg *Gut*. 1977; 18: 997- 1003.
[24] Wang, K. S. et al. Structure, sequence, and expression of the hepatitis delta (delta) viral genome. *Nature* 1986 ; 323, 508–514.
[25] Alfaiate D, et al. Delta virus: from biological and medical aspects to current and investigational therapeutic options. *Antiviral Res* 2015; 122 :112-29.
[26] Le Gal, F. et al. Eighth major clade for hepatitis delta virus. *Emerging Infect. Dis.* 2006; 12, 1447–1450.
[27] Wu, J. C., et al. Characterization and phylogenetic analysis of a novel hepatitis D virus strain discovered by restriction fragment length polymorphism analysis. *J. Gen. Virol.* 1998; 79 (Pt 5), 1105–1113.
[28] Casey, J. L. et al. Hepatitis B virus (HBV)/hepatitis D virus (HDV) coinfection in outbreaks of acute hepatitis in the Peruvian Amazon basin: the roles of HDV genotype III and HBV genotype F. *J. Infect. Dis.* 1996; 174, 920–926.
[29] Ibid. 19

- *Gammaherpesvirinae* composed of the genera Lymphocryptovirus (Epstein-Barr virus, EBV), infectious mononucleosis agent and Rhadinovirus (HHV-8), which remain latent in lymphocytes and some epithelial cells. They are mainly associated with malignant diseases of the lymphoid tissue.



Herpesvirus	Abbreviation		Size (kb)
	Common	Formal	
Alphaherpesvirinae			
Simplexvirus			
Herpes simplex virus type 1	HSV-1	HHV-1	152
Herpes simplex virus type 2	HSV-2	HHV-2	155
Varicellovirus			
Varicella-zoster virus	VZV	HHV-3	125
Betaherpesvirinae			
Cytomegalovirus			
HCMV	HCMV	HHV-5	227–236
Roseolovirus			
Human herpesvirus type 6	HHV-6	HHV-6	159–162
Human herpesvirus type 7	HHV-7	HHV-7	144–153
Gammaherpesvirinae			
Lymphocryptovirus			
EBV	EBV	HHV-4	172–173
Rhadinovirus			
Human herpesvirus type 8	HHV-8	HHV-8	134–138

Source : https://www.infectiologie.com/UserFiles/File/formation/du/grenoble/du-tai-grenoble-2022-23-cmv-r-germi-et-o-epaulard.pdf; Thèse Fleur Dupuy.

Human herpes virus 8 (HHV-8) may be involved in the pathogenesis of Kaposi's disease and Castleman's disease. As for human herpes virus 7 (HHV-7), its pathogenic role is still poorly defined. The prevalence of HHV-5 (CMV) is high: from 30% to 100% of people are infected with CMV depending on the region of the world considered. It is usually a minor infection. On the other hand, the severity of CMV infections during AIDS, after organ or hematopoietic stem cell transplantation, and during any disease requiring or resulting in significant cellular immunosuppression (lymphoma, prolonged corticosteroid therapy) justifies the use of antiviral, curative and preventive treatments[30].

4 ABL and SNG

The emergence of NGS or high-throughput sequencing in clinical microbiology is essential for new diagnostic and prognostic approaches in the field of infectious diseases. Traditionally, microbiological diagnostics have included a wide range of culture-dependent and non-culture-dependent methods. But today to detect, identify and characterize microorganisms, crucial steps for optimal patient care. Laboratories have access to multiple techniques for the direct detection of the responsible microorganisms, such as the culture of a biological sample, the detection of specific antigens or molecular biology (simplex or multiplex PCR, Sanger sequencing, high-throughput sequencing) and on the other hand indirect techniques such as infectious serology. This diagnostic arsenal is all the more interesting as we are seeing the emergence of new infections, favored by international travel and global warming, for which the use of innovative diagnostic methods is often a prerequisite. Among the strategies used in clinical microbiology, we can distinguish "shotgun" metagenomics, which is the only technique that currently allows panpathogenic and preconceived detection, i.e. of all the microorganisms potentially responsible for an infectious disease, including those still unknown.

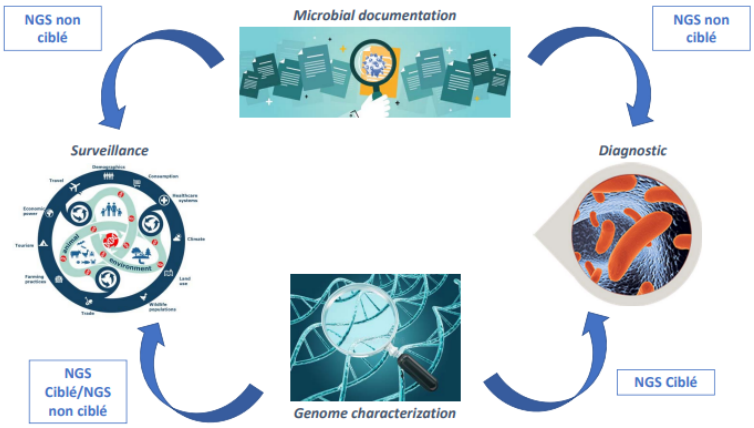
4.1 Quick reminder on the interest of the NSE in microbiology

The vast majority of infectious diseases present themselves in the form of syndromes that are most of the time weakly correlated with the nature of the pathogens responsible. Microbiological diagnosis is therefore of paramount importance in choosing the most suitable antimicrobial treatment for the microorganism responsible. But there is also a surveillance component that should be integrated into microbiological diagnosis.

While culture remains the "gold standard" for the etiological diagnosis of bacterial and fungal infections, it clearly shows its limits in viral infections. The contribution of molecular tests such as PCR, which are rapid and specific, but often presuppose a priori knowledge of the microorganisms suspected of being the cause of the infection, whether they are bacterial, viral, fungal or parasitic in nature. Hence the implementation of multiplex PCRs known as "syndromic". These approaches are based, for each infectious syndrome (respiratory, neuromeningeal, intestinal, etc.), on the simultaneous search for the main pathogenic microorganisms involved from a single sample. Although rapid and efficient, these approaches are limited by the number of pathogens targeted, and do not allow the identification of a variant, rare or emerging microorganism.

[30] Alain S, Cotin S, Hantz S. Cytomegalovirus resistance to antivirals. *Virology* 2009; 13(4):215-22.

The development of next-generation sequencing (NGS) in microbiology is paving the way for new approaches in the field of infectious disease diagnostics, as summarized by Prof. Rodriguez in the following figure. It highlights the two strategies adopted for the NSE in microbiology.

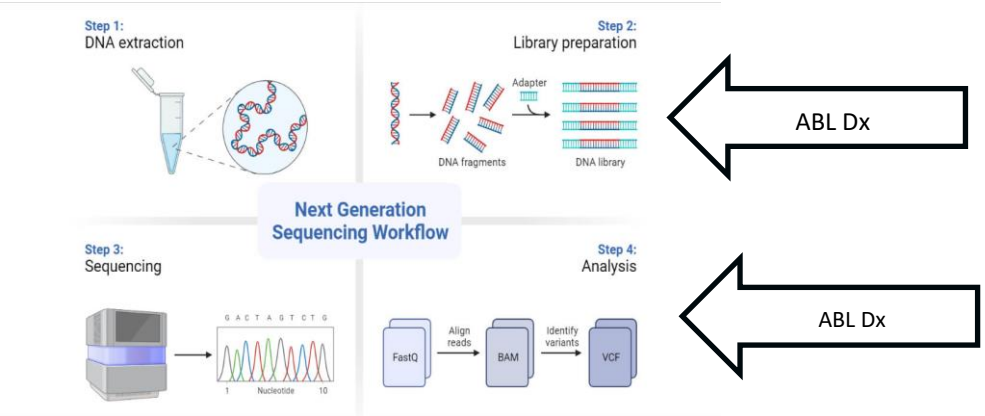


Source : https://www.infectiologie.com/UserFiles/File/formation/desc/2023/seminaire-mars-2023/t12-lundi-27.03/conf-3-apport-et-limites-c-rodriguez.pdf

The first approach is targeted NGS, which can answer relatively closed questions such as "is my patient's virus resistant?" To do this, it amplifies, and sequences one or more specific regions of a given genome(s), providing essential information for, for example, microbial identification (gene encoding 16S rRNA) or the search for resistance (gene(s) associated with viral resistance mutations), but also for the sequencing of small complete genomes such as those of viruses (e.g.: complete genome of SARS-CoV-2).
The second strategy consists of a non-targeted approach or "NGS shotgun". More global in its implementation, it is based on a random fragmentation of the nucleic acids present in a sample, followed by a sequencing of all the material. It is used either for the complete sequencing of large genomes such as those of bacteria or fungi from a culture (also called strain sequencing) or for shotgun metagenomics (SMg). The latter approach is based on the sequencing and analysis of all microbial genetic material (DNA + RNA) obtained from a biological sample and allows the identification of the microorganism(s) it contains for microbiological diagnostic purposes. When the quantity of sequences obtained is sufficient, it can also be used to reconstruct the complete genomes and thus characterize the microorganisms present in the initial sample, whether they are known or not yet described. Indeed, this "broad-spectrum" approach without preconceptions is capable of characterizing new microorganisms, and thus becomes essential in the context of the emergence of new infectious diseases [31]. Having new panpathogenic microbiological diagnostic tools without preconceptions could therefore increase the diagnostic capacities available to the clinician and improve the management of these infections.

4.2 SNG and ABL positioning

ABL Diagnostics has been able to grow across the entire value chain of routine diagnostics, in particular thanks to its innovative tests targeting some of the most important infectious diseases as well as its complementary



Source : https://microbenotes.com/next-generation-sequencing-ngs/

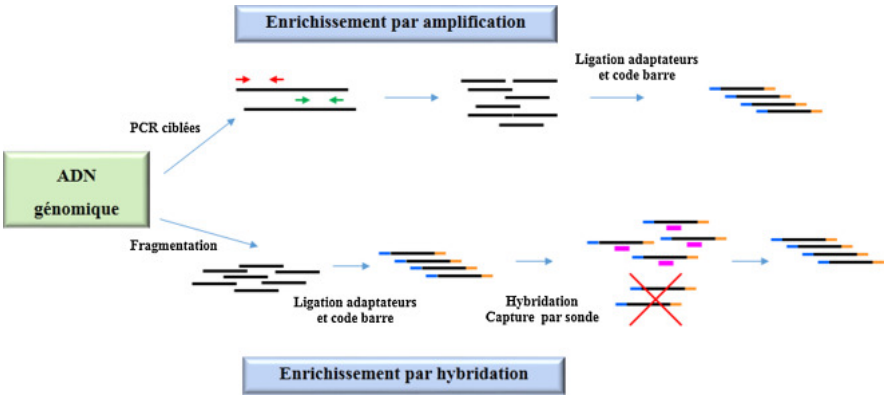
software. This approach is reinforced in the field of NGS, for which ABL's vendor-agnostic test kits can be used on a large number of DNA sequencing machines, including those offered by the largest suppliers (Illumina, ThermoFisher Scientific, MGISeq, Oxford Nanopore, PacBio, Element Biosciences). ABL can therefore target a

[31] M. Marani, et al. Intensity, and frequency of extreme novel epidemics *Proc Natl Acad Sci,* 2021 ; 118 (35)

larger number of laboratories. In addition, during the sequence of tasks to perform sequencing, which includes four main steps (see figure below): 1) preparation of the pre-analysis sample; 2) preparation of the bookstore; 3) the sequencing itself; 4) data analysis, ABL strives to be present on step 2 of preparing library preparation kits as well as on the supply of software for the data analysis stage

4.2.1 Preparation of libraries

This positioning is particularly relevant for the company, which by producing library preparation kits for SNG sequencing, is placed at an essential stage for the determination of the sequence. Indeed, the NGS requires an optimal and careful preparation of the genetic material upstream of the sequencing reaction, a guarantee of satisfactory results. In the vast majority of cases, nucleic acid extraction is not dependent on ABL. However, the first step is to produce millions of DNA fragments (copies of the areas of interest that we want to analyze). This collection of targeted and amplified DNA fragments is called a "library". Library constitution kits use two genomic DNA enrichment techniques. One is based on multiple PCR, i.e. the amplification of several fragments in the same tube, while the other is based on DNA capture. After generating fragments of 200 to 250 base pairs of genomic DNA by enzymatic digestion or sonication (ultrasound treatment), these after association with adapters and synthetic DNA barcodes, are hybridized with probes specific to the regions of interest (pink boxes in the figure below): this is the phenomenon of capture. The "uncaptured" fragments are eliminated.



Source : le séquençage d'ADN à haut débit en pratique clinique. Lacoste et al. Archi Pédiatrie 2017.

At the end of this step, we have a library made up of the enriched DNA regions that we wish to study, associated with a small sequence of synthetic DNA, equivalent to a barcode, identifying the original sample and thus allowing several patients to be sequenced at the same time, we then speak of multiplexing. Before any sequencing, clonal amplification of each "tagged" fragment is necessary. It allows us to significantly multiply the number of copies of each DNA molecule in the library (blue-black-orange fragments in our figure above). This amplification is carried out according to solid support platforms, which are then called "flow cells" or emulsions on isolated beads. The use of flow cells offers the possibility of sequencing directly on the support, whereas with beads, transfer to chips is required.

4.2.2 Analysis: DeepChek® Software Possibilities

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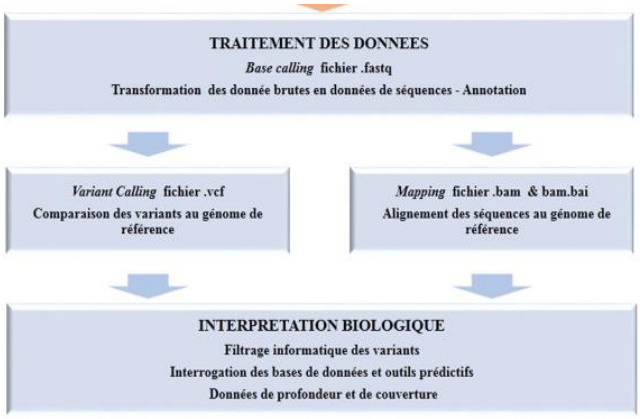
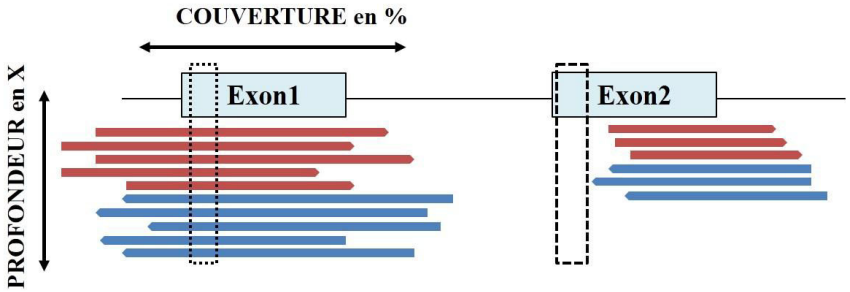
For step 4 of sequencing, i.e. the computer processing of the data from the NGS, specific bioinformatics algorithms have been created and implemented to manage the raw data, mainly SNG short reads, genotyping or subtyping, assembly of de novo genomes, detection of single nucleotide polymorphisms (SNPs) or mutations on amino acids, Chip Seq and RNA-Seq analysis were developed[32, 33] . First, it is necessary to transform the raw data into sequence data during a process called "base calling", which consists of assigning sequences and nucleotide bases to physical information (chromatogram peaks, electric current variation, light intensity variation, fluorescence). However, a series of filters based on data quality scores must be used in order to preserve the best sequenced fragments (the reads).

[32] Hatem, A. et al. Benchmarking short sequence mapping tools. *BMC Bioinformatics*, 2013, 14, 184
[33] Rucha M. et al. Computational analysis of next generation sequencing data and its applications in clinical oncology. 2018. https://doi.org/10.1016/j.imu.2018.05.003



Source : le séquençage d'ADN à haut débit en pratique clinique. Lacoste et al. Archi Pédiatrie 2017.

All the reads, after demultiplexing, are grouped together in a Fastq file. Demultiplexing has the effect of assigning each patient his or her sequences. Then, the sequences obtained are aligned and annotated on the reference genome, thanks in particular to alignment algorithms such as BWA (BurrowWheelerAligner), [34]which integrates a Burrows-Wheeler mathematical transformation. The results obtained after alignment are found in a SAM format which will then be converted into a . BAM, which is essential for calculating depth and coverage data for areas of interest. A few quick words on these two essential criteria for evaluating the quality of the NSE and the results obtained. First, the sequencing depth, which corresponds to the number of independent reads for each targeted database, expressed in the number of times (x). Thus, a depth of 20x, as recommended by the European Society of Human Genetics (ESHG),[35] means that the region of interest has been sequenced 20 times independently. Similarly, the coverage, expressed in %, corresponds to the percentage of fragments or bases actually sequenced in relation to the total number of fragments or bases to be sequenced initially. These results depend largely on the enrichment techniques used[36]. For routine clinical diagnosis, the cursor should be at 100% coverage with a minimum depth of 20x.



Source : le séquençage d'ADN à haut débit en pratique clinique. Lacoste et al. Archi Pédiatrie 2017.

The mapping data in the . BAM therefore give a good idea of the quality of the sequencing thanks to the depth and coverage data of the regions of interest. Then, the determination of all the patient's variants in relation to the possible reference genome with the data from the . VCF. At the end of this process, the biological interpretation step can be the most complex and delicate in order to reconcile genotypic sequences with phenotypic findings. The search for variants can then be carried out with software, allowing the annotation of SNPs as well as small referenced insertions and deletions. It is also possible to make a functional prediction of non-synonymous variants and identified splicing sites: all this information is found in the VCF file. Variants can be classified according to their estimated frequency in the general population and their theoretical pathogenicity to select the one or those potentially responsible for the pathology. Interpretation requires knowledge of the pathology, the gene and the functions of its products, based on human expertise and on the use of bioinformatics prediction tools and databases, but also data from the literature. Indeed, the amount of data from the SNG far exceeded the tools put in place in the framework of the first sequencing methods (cf. Sanger), just as the third generation sequencers have also led to the emergence of new algorithms adapted to longer reads and therefore to higher error rates[37].

5 Clinical utility of DeepChek® tests

The clinical usefulness of diagnostic and genotyping tests, with the advent of molecular biology, has become obvious, particularly in infectiology, in particular with the functional analysis of variants, one of the essential parts of the genetic analysis of pathologies. Indeed, the genome of microbes is subject to numerous mutations following

[34] Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. *Bioinforma Oxf Engl.* 2009 ; 25(14):175460.
[35] Matthijs G, et al. Guidelines for diagnostic next-generation sequencing. *Eur J Hum Genet*. 2016 Jan; 24(1):2-5.
[36] Mertes F, et al. Targeted enrichment of genomic DNA regions for next-generation sequencing. *Brief Funct. Genomics*. 2011 Nov; 10(6):374-86.
[37] Shanika L., et al. Opportunities and challenges in long-read sequencing data analysis. *Genome Biology*, 2020, 21:30

"operations" of maintenance of genetic material (replication, transcription, integration, etc.), which increases the rate of error and modification. While the vast majority of variants are non-functional and neutral, with no effect on the phenotype, some have an impact on the function and/or structure of proteins and can cause disease. It is therefore essential to set up variant selection filters to prioritize the variants most likely associated with the phenotypic traits observed.

5.1 Variant identification

This filter will make it possible to differentiate between variants that respond to therapies and those that are insensitive to them. The former are rare and have a strong impact on the regions coding the genes while the latter are more common in the population and are often located in the non-coding regions. Different criteria are used to classify variants, including frequency in the population, prevalence in affected individuals, segregation data, functional studies, type of variant, similarities to known variants, and computer predictions.

Viral strains are classified into genotypes and subtypes based on the percentage of nucleotide homology across the entire genome. Thus, in the case of HBV, strains with a divergence of less than 8% are of the same genotype and those with a divergence of less than 4% are of the same subtype[38]. Widely used during the Covid-19 health crisis, the identification of variants (subtype of virus differing from the reference virus by one or more mutations). Research and identification of variants are now essential to identify mutations of resistance or sensitivity to treatment. Indeed, the genomic profile of the virus allows the implementation of the right care protocol. This identification of variants can also be part of screening actions, particularly in cases of risky behavior for both HIV infections and viral hepatitis.

For example, what happens with HIV, described as a hyper-mutant virus with mutations resulting from retrotranscription errors, since reverse transcriptase makes an error every 10,000 bps in a 10,000 bps genome, i.e. one mutation every 10,000 bps! In addition, the daily viral production is 1011 virions produced and as many mutations in nearly 109 new infected cells. In addition, mutations are also observed in the infected cell on the APOBEC and vif proteins : APOBEC is a cellular protein that modifies the viral genome by introducing errors into it in order to make it inoperative and *lively*. Another phenomenon to be taken into consideration is the recombination of genetic material between different viruses.

5.2 Precision Therapy

Genotyping is part of personalized or precision medicine, which consists of a new approach to the therapeutic act based on a better understanding of the biological, genetic and now epigenetic characteristics of the patient. Genotyping allows genetic profiling of the patient or the pathogens involved (cancer cells, bacteria, viruses, fungi, etc.) in the disease. Genotyping or the search for human, viral or bacterial genetic variations makes it possible to generate catalogues grouping the different variants. While the search for variants in virology/bacteriology remains one of the primary applications of genotyping, advances in genomics, particularly on human genetic variations, have provided insight into common and rare diseases, accelerated the pace of drug development, and laid the foundation for the future of precision medicine. Genotyping also allows the study of complex genotype-phenotype relationships in studies focusing on single nucleotide polymorphisms (SNPs), insertion/deletion polymorphisms, and copy number variants (CNVs).

The genotyping tests offered by ABL Diagnostics are part of the development of precision medicine, in particular by integrating the multiple dimensions of clinical and molecular data of the health and well-being of individuals (see DeepChek® software NADIS® solution). In addition, there is an improvement in methods for extracting and discovering clinical phenotypes from electronic medical records[39]. Deconvolving information from genotype to pathological state often involves intermediate phenotypes.

Personalized medicine aims to allow a dynamic and quantitative representation of the "GPS coordinates" of a patient's health, estimated from multiple modalities of personal health data. Medicine is gradually moving away from the traditional model of reactive patient care towards well-being and lifelong learning health care systems aim to prevent individuals from disrupting their individual biology towards disease states.

5.3 Therapeutic resistance

It is the great genetic variability of HIV, which has led to the very frequent appearance of mutations in the viral genome, particularly in the genes targeted by antiretrovirals[40]. If viral replication occurs in the presence of antiretrovirals, it often leads to the development of antiviral resistance. Resistant mutants, which existed before the initiation of the therapy, are quickly selected, and tend to become the predominant viral population[41]. Thus, the speed with which mutations are brought to the fore will depend strongly on the antiretrovirals used. Thus, for

[38] Kramvis A, et al. Relationship of serological subtype, basic core promoter and precore mutations to genotypes/subgenotypes of hepatitis B virus. *J Med Virol.* 2008; 80(1):27-46.
[39] Newton KM, et al. Validation of electronic medical record-based phenotyping algorithms: results and lessons learned from the eMERGE network. *Journal of the American Medical Informatics Association : JAMIA.* 2013;20:e147–154.
[40] Abram ME, et al. Nature, Position, and Frequency of Mutations Made in a Single Cycle of HIV-1 Replication. *J Virol.* 2010 ; 84(19):9864.
[41] Tang MW, Shafer RW. HIV-1 Antiretroviral Resistance: Scientific Principles and Clinical Applications. *Drugs*. 2012 ; 72(9):e1.

a weak genetic barrier, a single mutation will be enough to give the virus a high level of resistance, while for others with a high genetic barrier, it is the accumulation of mutations that will generate resistance. Resistance, which can be crossed with several molecules within the same therapeutic class. The best prevention of the development of resistance is to achieve an undetectable plasma viral load quickly and sustainably.

5.3.1 HIV, the ultra-mutant virus

The genetic variability of HIV-1, a major characteristic of RNA viruses, is due in particular to intense viral replication[42], a high rate of recombination[43] and a high error rate of viral RT (reverse transcriptase) which does not have an error correction system. HIV-1 is currently subdivided into four groups: the M or Majority group and three other minority groups: O for Outlier, N for non-M, non-O and the P group. Group M is itself subdivided into nine subgroups from A to K and 55 recombinant forms, CRFs or Circulating Recombinant Forms, the number of which continues to grow. There is a 20 to 30% nucleotide difference in the *env gene* between the subgroups and 14% for the gag gene. Similarly, within a subgroup, variability exists in the range of 5 to 20%.

Thus, in France, subtype B is the most represented. On the other hand, for non-B subtypes, it is the protease gene that shows variability and can therefore present substitutions on certain key targets considered as resistance mutations in the B subtype. For etravirine and rilpivirine, about 10% of the non-B subtypes have at least one mutation[44]. Similarly, for subtype C, mutation profiles have been identified inducing high-level resistance to NNRTIs. This is the case of the V106M mutation. In addition, there is an emergence of phenotypes resistant to tenofovir in this subtype[45].

This is why the work of Prof. Morlat's expert group has made it possible to issue recommendations for the prescription of a genotypic resistance test:

- When HIV infection is diagnosed or when the last available sample is taken before starting treatment. Precise identification of the HIV-1 subtype should accompany the first genotyping result.
- In the event of virological failure, ensuring that the patient is still on ARVs at the time of collection.

Tropism determination and integrase gene analysis should only be performed if treatment with target molecules is considered.

Classe des antirétroviraux	Mécanisme de résistance	Mutations	Molécules touchées
Inhibiteurs nucléosidiques et nucléotidiques de la transcriptase inverse (INTI)	Excision de l'analogue nucléosidique par les mutations appelées TAMs : Favorisent l'accès de l'ATP au site de polymérisation qui réagit avec l'analogue nucléosidique en le détachant de la chaîne d'ADN viral en formation	M41L, D67N, K70R, L210W, T215Y/F et K219Q/E	Résistance progressive à l'ensemble des INTI à des niveaux divers
	La diminution d'incorporation des nucléosides ou nucléotides artificiels au profit de nucléotides naturels	M184V	Lamivudine (3TC), Emtricitabine (FTC)
		K65R/N/E	Ténofovir disopropyl fumarate (TDF), l'abacavir, didanosine
		L74V	Abacavir, Didanosine
Les inhibiteurs non nucléosidiques de la transcriptase inverse (INNTI)	Mutation empêchant le blocage de la transcriptase inverse par fixation au niveau d'une poche hydrophobe proche du site actif de l'enzyme. Une seule mutation entraine une résistance de haut niveau à **l'INNTI** et des résistances croisées	K103N	INNTI + Efavirenz, Névirapine
		Y181C	INNTI + Efavirenz, Névirapine, Rilpivirine
		E138K	
		M184I	Association Rilpivirine, Lamivudine, Emtricitabine : Renforcement de la résistance (37)
Inhibiteurs de Protéase	Mutations situées au niveau du site actif de l'enzyme ou à distance de celui-ci. Phénomène graduel avec accumulation progressive. Mutation au niveau des sites de clivage du gène gag : Résistance in vitro (38)	I50L	Atazanavir, pas de résistance croisée
		A431V, V362I (gag)	Impact sur de nouvelles molécules en cours de développement : BMS-955176 (39)
		K20I, K70R et L89M	Impact de la réponse virologique sur les VIH-1 non B
Les inhibiteurs de fusion	Mutations du domaine HR1 de la gp41	AA 36 à 45	enfuvirtide
Antagoniste CCR5	Mécanisme d'échappement viral avec émergence de sous-population X4 minoritaire à l'instauration du traitement ou émergence de virus R5 (40)	Analyse génotypique en cours d'études	Maraviroc
Inhibiteurs d'intégrase	Sélection par les 3 profils de mutations majeures	N155H, Y143C/H/R, Q148K/R/H	Raltégravir, Elvitégravir : présentent une résistance croisée quasi absolue (41)

Source : Séquençage du VIH :apport du NGS en routine et comparaison avec la méthode Sanger Thomas Lhossein

[42] Ibid. 36
[43] Levy DN, et al. From the Cover: Dynamics of HIV-1 recombination in its natural target cells. *Proc Natl Acad Sci U S A.* 2004 ; 23; 101(12):4204.
[44] Lambert-Niclot S, et al. Prevalence of pre-existing resistance-associated mutations to rilpivirine, emtricitabine and tenofovir in antiretroviral-naive patients infected with B and non-B subtype HIV-1 viruses. *J Antimicrob Chemother.* 2013; 68(6):1237-42.
[45] Lukashov VV, Goudsmit J. HIV heterogeneity and disease progression in AIDS: a model of continuous virus adaptation. AIDS Lond Engl. 1998; 12 Suppl A:S43-52.

The resistance of HIV to different therapeutic molecules is currently assessed using two distinct approaches: phenotypic tests and genotypic tests. Phenotypic tests based on the use of recombinant viruses obtained from the patient's plasma RNA sample provide an antivirogram[46]. This test, which is conceptually very similar to the antibiogram, makes it possible to determine the concentration of the antiviral inhibiting 50% and 90% of viral multiplication (IC50 and IC90). ABL's core genotypic tests make it possible to identify, by sequencing, the mutations present in the genes of interest (see above). The reference method remains the Sanger technique, which with a depth of 20% detects the presence of major mutations (20% or more presence). On the other hand, the NGS, with capacities of around 0.1 to 1%, offers increased detection capacities, particularly for minority viral populations.
As can be seen in the table above, which shows the impact of the HIV-1 subtype on antiretroviral resistance, a large number of mutations (3rd column) affect a large number of viral functions inducing phenotypic changes resulting in resistance.

The study of resistance (or genotypic test) by sequencing is now a key step in the therapeutic strategy for HIV. It is indicated in several clinical situations requiring the search for mutations in the reverse transcriptase, protease and integrase genes, or even glycoprotein 120. The recommendations are identical between an adult and a child: 1) during the primary infection or before initiation of treatment. (AII); 2) in virologic failure (2CV > 50 copies/ml) (AII) 3) in case of post-exposure prophylaxis (BIII). A recent consensus conference bringing together the ANRS (National Agency for Research on AIDS and Viral Hepatitis), the CNS (National Council for AIDS and Viral Hepatitis) and a group of French experts led by Prof. Morlat published a report explaining the different mutations found that can interfere with treatments. The different classes of antiretroviral drugs (ARVs):

- Nucleoside inhibitors reverse transcriptase (INTI) [*AZT*, Retrovir® ; *D4T*, Zerit® ; *abacavir*, Ziagen®, la *didanosine* (ddl, Videx®), la *lamivudine* (3TC, Epivir®).
- non-nucleoside reverse transcriptase inhibitors (NNRTIs): *nevirapine* (NVP, Viramune®), *efavirenz* (EFV, Sustiva®), *etravirine* (ETR, Intelence®) and *rilpivirine* (RVP, Edurant®).
- Protease inhibitors (PIs): *saquinavir* (SQV, Invirase®), *indinavir* (IDV, Crixivan®), *nelfinavir* (NFV, Viracept®).
- integrase (II) inhibitors: *raltegravir* (RAL, Isentress®) and *elvitegravir* (EVG, Vitekta®) and *dolutegravir* (DTG, Tivicay®) is a second-generation inhibitor.
- Fusion inhibitors.
- The anti-CCR5.

There are more and more limitations in the study of viral RNA alone. Indeed, the quantification of proviral DNA is an essential marker for developing mitigation strategies. This makes it possible to measure the residual viremia in the host reservoirs, which are numerous: any cells or tissues hosting the integrated forms of HIV, the main ones being CD4+ T lymphocytes, monocytes/macrophages and then the secondary lymphoid tissue[47]. A low level of HIV-DNA is associated with virological success during dual therapy strategy, especially when using 2 NNTIs[48].
One of the problems that can arise in therapeutic relief is that even with proviral DNA at its lowest, it is not possible to predict effectiveness in the strategy[49]. However, viral DNA still remains a quantitative and informative marker on the patient's infectious status and may be relevant in patients with virological failure. However, systematic genotyping is not recommended because of the risk of detecting irrelevant mutations as well as not finding resistance mutations during previous genotyping. There is a lack of standardization in the different genotyping methods. There are different algorithms for interpreting HIV-1 resistance, such as Stanford, used by English speakers, and the ANRS v31 in France. The exhaustive list of changes of interest is available on the ANRS website[50].

5.3.2 Mycobacterium: A very resistant complex

The *mycobacterium* complex can become resistant to antimicrobials used to treat and cure tuberculosis. It is the selection of resistant mutants during the treatment of pulmonary tuberculosis has been recognized as a major cause of failure since the first uses of streptomycin as early as the 50s. However, the same phenomenon is taking place with the new generations of anti-tuberculosis drugs, particularly when used as monotherapy: isoniazid (INH), rifampicin (RMP), ofloxacin. This "acquired" resistance to antibiotics is almost always the consequence of mutations in chromosomal genes. Acquired because there are naturally and spontaneously, due to genetic variability, within a wild population of *mycobacterium*, a certain number of mutant bacteria resistant to each of the anti-tuberculosis drugs in proportions varying from 1/105 mutant resistant to INH to 1/107 for RMP and ofloxacin.

Thus, within a tuberculous sample containing 108 bacilli, there are, before treatment, at least 1,000 INH-resistant bacilli and 10 RMP-resistant bacilli. For there to be double mutants resistant to both isoniazid and rifampicin, the occurrence of such an event would have to be rare or even impossible (probability of an independent mutation multiplied by the probability of the other equally independent mutation: 1/105 × 1/107 = 1/1012). The

[46] Wang K, et al. Antivirogram or PhenoSense: A comparison of their reproducibility and an analysis of their correlation. *Antivir Ther.* 2004; 9:703-12.
[47] Avettand-Fènoël V, et al. Total HIV-1 DNA, a Marker of Viral Reservoir Dynamics with Clinical Implications. *Clin Microbiol Rev2016; 29(4):859*-80.
[48] Prazuck T, et al. Long-term HIV-1 virologic control in patients on a dual NRTI regimen. *HIV Clin Trials.* 2013; 14(3):120-6.
[49] Chun T-W, et al. Rebound of plasma viremia following cessation of antiretroviral therapy despite profoundly low levels of HIV reservoir: implications for eradication. *AIDS Lond Engl.* 2010; 24(18):2803-8.
[50] HIV French Resistance - HIV-1 genotypic drug resistance interpretation's algorithms [Internet]. [cité 11 oct 2021]. Disponible sur: http://www.hivfrenchresistance.org/

combination of the two antibiotics prevents the selection of mutants resistant to each of them[51]. Despite the rarity of the phenomena, we have seen the emergence of new drug resistances. Primary resistance that has acquired at least one resistance to one of the treatment standards (INH, RMP) is considered multidrug-resistant (MDR). More recently, secondary resistance in MDR strains, which have been shown to be resistant to the most effective second-line antibiotics such as fluoroquinolones and one of the reserve aminoglycosides (amikacin, kanamycin, capreomycin). These resistances are therefore considered to be ultra drug-resistant strains (XDR).
Acquired resistance most often affects isoniazid for nearly 30% of global cases and nearly 50% of cases in Eastern Europe. However, the number of MDR/XDR remains constant with [52]nearly 410,000 cases in 2022 compared to 440,000 cases in 2008 recorded by the WHO[53].

5.3.3 A multiplicity of liver viruses

Hepatic viruses are an important corpus of viruses inducing extremely serious, chronically evolving liver diseases. This family of viruses has exclusive or predominant hepatic tropism, which leads to liver damage and viral hepatitis. However, in some acute episodes, the main diagnoses to be made are those of HAV and HBV. However, HCV and HEV can be considered as a second-line treatment. This viral richness with at least five distinct viruses and as many variants means that liver viruses are found in the general population in a very diffuse way, since the WHO estimates that there are nearly 2 billion people infected with HBV and nearly 250 million chronic carriers of HBsAg.

5.3.4 A diversity of organic targets for herpesviruses

The emergence of resistant CMV strains is a particularly important concern in immunosuppressed or immunocompromised individuals[54]. This resistance usually occurs during prolonged exposure of a few weeks to a few months and is characterized by the maintenance of the viral load or disease despite drug therapy[55]. It affects nearly 5% of organ or hematopoietic stem cell recipients, and represents an unfavorable factor in the evolution after transplantation. As can be seen in the table below.

Organ	Infection	Disease
Kidney	8%–32%	8%
Heart	9%–35%	25%
Liver	22%–29%	29%
Lung or heart/lung	39%–41%	39%
Pancreas or kidney/pancreas	50%	50%

Adapted with permission from McDevitt LM. *Am J Health Syst Pharm.* 2006;63:S3–S9.

Source : Prise en charge des infections à HSV, VZV et CMV (infectiologie.com)

The main antivirals used for CMV are *ganciglovir*, its prodrug, *valganciclovir* (VGCV), *cidofovir* (CDV), and *foscarnet* (Hamilton, 2012). The response to treatment usually results in an undetectable viral load within three weeks[56]. Non-response may be explained by virological (resistance) and pharmacological factors (under-dosing of the antiviral or poor penetration at the site of infection) or may be caused by immunosuppression. The search for mutations in resistance to antivirals already received by the patient makes it possible to distinguish non-responders or slow responders (with a high risk of relapse) from true virological resistance, and to adapt the antiviral treatment. Mutations in the UL97 gene (protein kinase) or the UL54 gene (polymerase) confer the main resistances to previous antivirals. Mutations in the UL97 gene are linked to resistance to GCV and VGCV cross-linked with *aciclovir* and its prodrug *valaciclovir*. Later mutations in the UL54 gene can lead to cross-resistance to GCV and CDV, resistance to FOS, or cross-resistance to all three antivirals.

5.3.5 Oncology

The study of the human genome and genes has profoundly modified and certainly revolutionized oncology. Indeed, the "exhaustive" mapping of genes has made it possible, thanks to a better understanding of the locations and regulatory mechanisms, to approach the mechanisms of cancerization as closely as possible. These techniques make it possible to act on several levels:

- Classification of cancers.
- The use of genes as biomarkers, diagnosis.
- Prediction and monitoring of treatment responses.

[51] Veziris, N & Robert, J. Resistance to anti-tuberculosis drugs and therapeutic impasse. *Med Sci.* 2010;26:(11):976-980.
[52] 1.3 Drug-resistant TB (who.int)
[53] World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response 2010, Genève, 71.
[54] Drew,L W. Cytomegalovirus resistance testing: pitfalls and problems for the clinician. *Clin Infect Dis.* 2010 ; 50(5):733-6.
[55] Kotton, C N. Management of cytomegalovirus infection in solid organ transplantation. *Nature Reviews Nephrology* 2010; 6: 711–721.
[56] Alain 2009

- Adaptation to treatments based on genetic mutations;
- Development of new drugs targeting specific genetic changes

Also, the relevance of genotypic diagnosis, which looks for genetic mutations within the genome, is no longer to be demonstrated in oncology, because these point transformations within genes (SNPs) play an essential role in survival, in particular the notion of hotspot. This search for somatic mutations in hotspots of a number of genes such as those that can be found listed in the Catalogue of Somatic Mutation on Cancer (COSMIC) database. It is the most detailed and comprehensive resource for exploring the effect of somatic mutations in human cancer. The latest version, COSMIC v100 (May 2024), which has just added 307,772 new variants, bringing the total number to more than 24 million, including 120,033 new coding mutations across 1.4 million tumor samples, curated from more than 26,000 publications. In addition to coding mutations, COSMIC covers all the genetic mechanisms by which somatic mutations promote cancer, including non-coding mutations, gene fusions, copy number variants, and drug resistance mutations. COSMIC is mostly managed manually, which ensures quality, accuracy, and descriptive data entry.

6 The regulation and its corollary, reimbursement

The regulatory aspect, as well as reimbursement, play a critical role in the use and integration of new diagnostic products. ABL Diagnostics is targeting its domestic market as well as other markets such as the United States and China. For each of these markets, the regulatory process is unique to allow for the implementation of the refund

6.1 The regulatory

The lines governing regulatory positions, whether in Europe or the United States, are moving. With the implementation of a new European IVDR directive to replace the IVDD, with the overhaul within the FDA of the LDT and CLIA statutes, until now cornerstones of the development of innovative tests in the USA.

6.1.1 The European situation

ABL Diagnostics is a legal manufacturer of reagents, while ensuring their design, development, production, storage, marketing, support and maintenance. It is therefore only natural that the Marseille site, where all these activities take place, has been ISO 13485 certified since October 2022. This internationally recognised standard establishes the requirements for a quality management system specific to the medical device sector: a step often prior to CE marking. The company wishes to obtain the ISO 13485 standard for the software part on its Luxembourgish.

ABL Diagnostics is subject to the new European IVDR regulation (Regulation (EU) 2017/746. The company has several tests and software that have already received the CE mark. The main differences between IVDD and IVDR are greater evidence of clinical benefit versus risk, more complex compliance assessment, and higher traceability requirements. In addition, there should be an increased involvement of notified bodies. The IVDR Directive also introduces a new classification of IVD devices into 4 risk classes:

- Class A: Low risk to patients and public health
- Class B: moderate individual risk and/or low risk to public health
- Class C: high individual risk and/or moderate risk to public health
- Class D: high individual risk and high risk to public health.

The IVDR also proposes a clarification of the obligations of economic operators (manufacturers, authorized representatives, importers and distributors) as well as increased transparency thanks to the information made public in a new European database on medical devices (EUDAMED). Thus, the key issue that remains is the EU's transition from the IVDD Directive (IVDD) to the IVD Regulation (IVDR). The IVDR came into force in May 2017 with a five-year transition period. But since then, several changes have taken place, the most recent of which was in January 2024. Indeed, the European Commission has published a proposal to amend the IVDR extending the transition periods. While the date of 26 May 2022 remains the date of application of this new European regulation, the extension of the deadlines offers manufacturers and notified bodies more time to pass IVD products through the IVDR conformity assessment.

The previous figure attempts to summarize the regulations for transitional periods under the IVDR, which only apply to existing products already on the market, declared compliant before 26 May 2022 and which belong to classes D, C, B or A (sterile) according to the IVDR. As can be seen, the duration of the new deadlines depends on the future risk class of the IVDD and whether a notified body has already been involved in the IVDD.

Source : https://blog.iohner-institute.com/regulatory-affairs/ivdr-transitional-

ABL Diagnostics, which has 8 candidate tests for IVDR, 3 of which are in class C (rule 3(k): relating to genetic tests) and 5 in class A (rule 5: General laboratory products, culture media) should therefore not benefit from this extension of time for its class A products, but on the other hand for its class C products, The Company has until December 31, 2028.

6.1.2 The American situation

One of ABL Diagnostics' goals is certainly to approach the American market and grow there. But for this to happen, the company will have to obtain a status compatible with the marketing of its tests on the laboratory developed test (LDT) market. However, although this market is less regulated, it is subject to increasingly restrictive regulatory steps. Indeed, on April 29, 2024, the Food and Drug Administration (FDA) published its final rule confirming the Agency's position that lab-developed tests (LDTs) are in vitro diagnostic products (IVDs) regulated as medical devices under the federal Food, Drug, and Cosmetic Act (FDCA). This transformation of the FDA's initial rule for LDT should also have an influence on the algorithms developed with these LDTs, which until now were considered differently from SaMDs (Software-as-Medical Devices). This final rule could lead ABL Diagnostic to capitalize on its ISO 13485 certification to make a 510(k) request, which is expected to take about six months. In addition, if a product is considered to have a unique position in the market, ABL Diagnostics said it could evaluate a PMA procedure. Otherwise, ABL Diagnostics will have to seek MDSAP certification for its quality management system, which facilitates the registration of its products in the United States, Canada, Brazil and other countries (Japan, Australia).

6.2 Repayment

The integration of genomic testing (genotyping, NGS) into clinical practice is an opportunity to improve patients' lives, especially as it offers the possibility of optimizing the effectiveness of drugs and/or minimizing the risk of adverse effects. In order to ensure equal access for as many patients as possible to these innovative and individualized proposals, their costs should be reimbursed by the respective national health systems. To do this, it is necessary to evaluate these tests in the best possible way, both in terms of clinical effectiveness and total economic cost. For this reason, payers evaluate new diagnostic products based on three factors:

- Analytical validity: the accuracy and reliability of the test when it comes to sequencing specific variants, for example the Alzheimer's disease gene.
- Clinical validity: the degree of correlation with a clinical outcome.
- Clinical utility: whether the test provides a better understanding and improves cost-effectiveness.

The reimbursement environment for sequencing-based methods (Sanger, SNG) has long been uncertain, even though healthcare payers saw it as an attractive way to improve the understanding of genetic diseases, responses to treatments, and disease prognosis. However, in recent years, thanks in particular to the health crisis, which has "trivialized" the use of these methods, the levels of reimbursement and coverage have increased, as has the number of NGS tests over the last ten years. Overall, we see that sequencing technology is booming, so more and more tests are entering the bill of materials and are eligible for reimbursement.

Following the example of what was achieved during the Covid-19 epidemic, the reimbursement of COVID detection tests has evolved continuously and differently depending on the country and the pandemic periods, with fewer reimbursements in the post-covid period. During the crisis, a large repayment was in force. To date, tests are still reimbursed but conditional on certain types of patients only (hospitalized with symptoms...):

- Health insurance covers 70% of the cost of the test if it is carried out by a doctor or pharmacist and 60% if it is carried out by a nurse.
- The most vulnerable people continue to benefit from full coverage by the Health Insurance. These are patients with long-term illnesses, people over 65 years of age, minors, professionals in the medical and medico-social sectors, people benefiting from an exemption under maternity insurance and those subject to collective screening.

For HIV infection, the reimbursement of genotyping tests by sequencing also varies greatly from country to country. The main HIV test is reimbursed in the vast majority of countries, including France of course, with rates ranging from 350 euros to nearly 1000 euros, depending on the technology (Sanger or NGS) used, and the genes covered (RT, PR, INT of HIV).

	Cotation	Tarif en €	Prise en charge ou Hors nomenclature
GENOTYPE HCV	HCVGENO_B	350	91
HIV INTEGRASE	INTRP-B	270	70.2
HIV TROPISME	HIVF_B	550	143
HIV RESISTANCE RT/PR	HIVRES-B	1300	338
HCV RESISTANCE	HCVRES_B	202	52.5
HBV RESISTANCE	HBVRES_B	202	52.5

Source : présentation ABL Diagnostics.

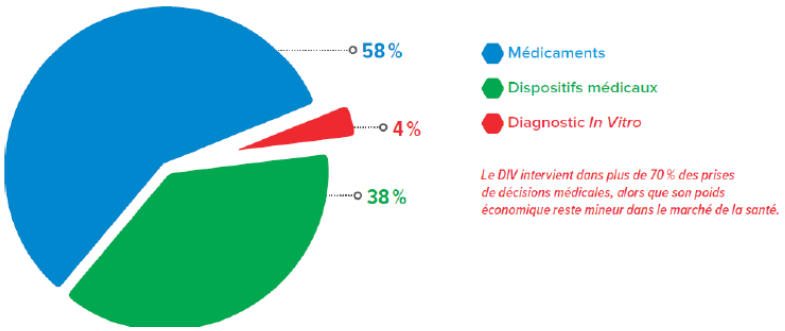
Developed countries now have good reimbursement coverage for most of ABL Diagnostics' products (see table below), and this situation continues to improve due to increased incidence rates in targeted indications, increased awareness, and technological improvements. We therefore believe that the reimbursement landscape is promising for ABL Diagnostics in the coming years.

7 Favorable Trends for the Diagnostics Industry

The examples of HIV and infectious diseases illustrate the evolution of IVD. Indeed, since its emergence in the early 1980s, HIV has been monitored through diagnosis, from its isolation and identification by physical methods (microscopy or electron microscopy), through direct detection techniques (markers, antibodies), then indirect detection with serological tests (ELISA detection of antibodies produced by the patient's immune system). There are even 4th generation ELISAs that detect both the antigens of the virus and the patient's antibodies. The principle of antibody detection is the basis of the rapid tests and HIV self-tests available in pharmacies. But in the 90s, the development of molecular biology made it possible to go back to the source, i.e. DNA and RNA. PCR techniques and its variants (RT-PCR, q-PCR) have increased the sensitivity of detection as well as the specificity of the information obtained faster than any other method. For example, it is now possible to detect and quantify an HIV viral load at thresholds below 100 RNA copies/mL of blood. However, these molecular approaches are only made possible by prior knowledge of the genome sequence of the pathogen sought, and become unsuitable for the detection of new or unexpected infectious agents.

7.1 The IVD in France, Europe and the world

One of the consequences of the COVID-19 pandemic has certainly been the emphasis on diagnostics and even more so *on in vitro* diagnostics (IVDs). Indeed, IVD tests play an essential role in the care pathway, by allowing the doctor to guide his therapeutic decisions according to analysis results obtained from the patient's samples (blood, urine, biopsies or other). Its economic weight remains a minority (4%) compared to the heavyweights of the health industries, which are medicines and medical devices. On the other hand, its crucial role has been well underlined by a recent publication by the SIDIV (Union of *In Vitro*[57] Diagnostic Industries), which shows that IVD is used in about 70% of medical decision-making in community medicine and in more than 80% in hospitals.



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Source : Diagnostiquer les maladies infectieuses à l'ère de la génomique, Philippe Pérot, DUGBM 2018.

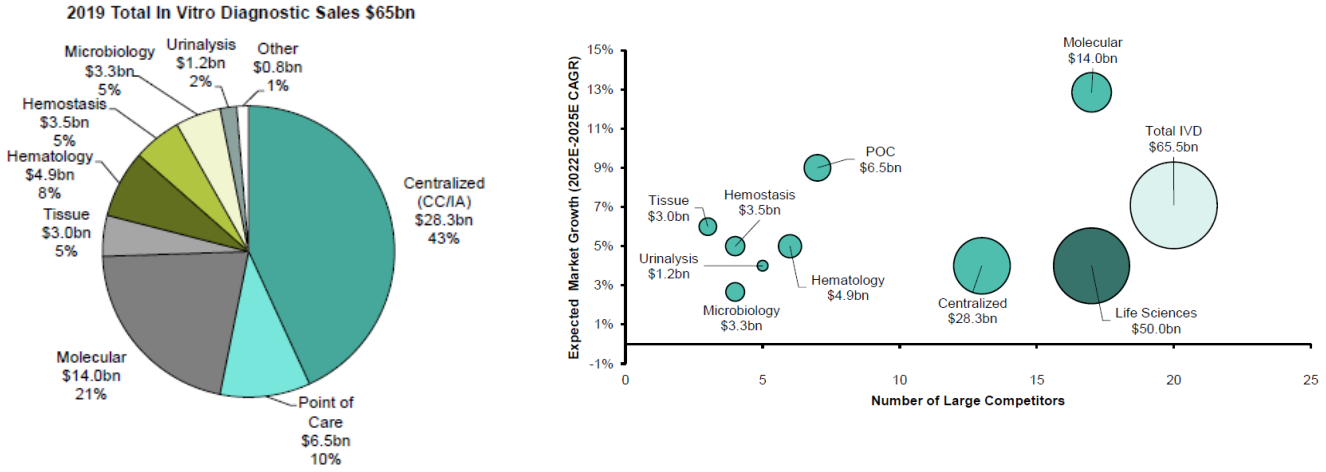
Source : http://siphif.org/wp-content/uploads/2017/07/BS-6-SIDIV.pdf

With this central place in therapeutic decisions, the IVD is therefore involved throughout the patient care pathway: from screening to follow-up, including the stages of diagnosis, prognosis, eligibility for treatment and treatment. Recent developments in molecular diagnostics reinforce this positioning closer to the new precision medicine by detecting or preventing risks, selecting treatments according to the patient profile, prognosticating changes and/or responses to treatment, always in the light of patient information. New genomic and genetic technologies now make it possible to evaluate and monitor the response to treatments, always according to the genetic profile of the patient or the pathogen.

With a turnover of €2.6 billion, France is the second largest in Europe behind Germany and ahead of Italy. By achieving 65% of their turnover from exports, the hundred or so companies, 90% of which are SMEs and VSEs in the field, represent about 12,000 direct jobs in the region. With revenues of €20.670 billion in 2021, the European market has largely benefited from the health crisis, as its growth has been multiplied by 72 and 103 respectively between 2019 and 2021, from €11.1 billion in 2019 to €14.3 billion (2020) and €20.6 billion in 2021[58].
The growing global *in vitro* diagnostics (IVD) market was worth $65 billion in 2019, according to a study by the investment bank Bernstein in 2021. Growth estimates would bring it to $95 billion in 2025, an average annual growth rate of 3%.

7.1.1 Molecular diagnostics, a growth vector

When we take a step back to look at the IVD market, we see that it is segmented into a multiplicity of sub-segments, which are declined either according to the technologies, or according to the object of analysis, or according to the analysis carried out.



Source : In Vitro Diagnostics : The lifeblood of modern medicine ; Bernstein, 2021.

As can be seen in the figure above, the main segments are centralized testing ($28.3 billion, 43% of the total volume), molecular diagnostics with $14 billion and 21% followed by point-of-care at $6.5 billion and 10% market share. ABL Diagnostics targets two distinct sub-segments with its technologies: microbiology, with a relatively low growth rate and a significant turnover of $3.3 billion, and molecular IVD, driven by an expected growth rate much higher than the other segments, at ~13% over the period considered 2022-2025. However, this sustained growth attracts covetousness, since the competitive intensity is also strong with more than fifteen competitors that are important in size.

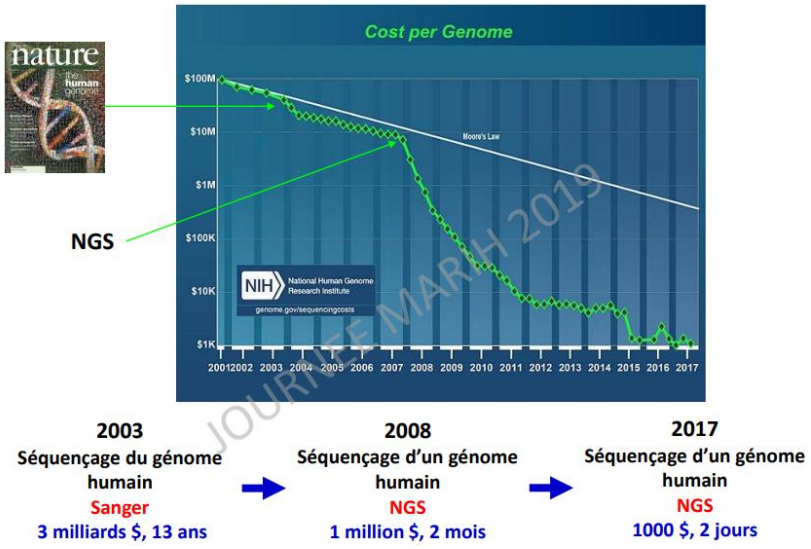
[58] https://www.medtecheurope.org/wp-content/uploads/2022/12/european-ivd-market-report-2022.pdf

7.1.2 Genotyping: at a crossroads

Analyses of the genotyping market are somewhat contradictory, but all acknowledge that the annual growth rate of this sub-segment will be significant. According to Business Research Insights, with a CAGR of 19.3%, the market for genotypic testing is expected to grow from $26.62 billion in 2022 (much higher than the $14 billion molecular IVD) to $129 billion in 2031. Data Bridge Market Research also shows impressive figures, but still more moderate, with a market that would grow from $15.1 billion in 2022 to $23.7 billion in 2030 with a CAGR of 14.59%. For Grand View Research, the CAGR is in the range of 14.59% between 2023 and 2030 but would take the market from $15.1 billion in 2022 to. According to Precedence Research, the global genotyping market size accounted for $19.41 billion in 2023 and is expected to exceed $75.60 billion by 2033, with a CAGR of 14.53% during the forecast period of 2024 to 2033.

7.1.3 Next Generation Sequencing

The next-generation sequencing (NGS) market size is expected to reach $34.75 billion by 2031, up from $10.00 billion in 2023. CAGR of 16.8% from 2023 to 2031. Increasing throughput and reducing costs will likely remain the key trends in the market. Increasing throughput and reducing costs are strong trends in this market. Indeed, constant and recent improvements in sequencing techniques have not only allowed technological improvements, but also allowed precision medicine to be a model for the prevention, diagnosis and treatment of diseases, particularly implemented for the treatment of cancer. Several companies have produced strategic developments that support the growth of the market. So, in 2022, Illumina launched NovaSeq X Series to generate more than 20,000 whole genomes per year. The same year, Ultima Genomics launched into short-read sequencing and announced the genomic sequencer at $100. At the same time, a new class of DNA sequencing has emerged, called third-generation sequencing (TGS), which can sequence single DNA molecules without amplification and allow the construction of "reads" much longer than NGS. Each technology can produce very long reads of up to 15,000 bases from single DNA and RNA molecules.



Source : https://marih.fr/wp-content/uploads/2019/12/3_20196_marih_ngsneu_vf.pdf

The recent WHO recommendations (March 2024), on the use of a new class of diagnostic technologies, targeted NGS tests for the diagnosis of drug-resistant tuberculosis (TB), integrated into the updated TB guidelines are expected to have a positive influence on the use of the NGS. In fact, the new WHO TB sequencing portal with more than 56,000 sequences (https://www.who.int/news/item/20-03-2024-who-launches-new-guidance-on-the-use-of-targeted-next-generation-sequencing-tests-for-the-diagnosis-of-drug-resistant-tb-and-a-new-sequencing-portal) will contribute to the collective understanding of mutations in the Mycobacterium tuberculosis genome and their association with drug resistance.

7.2 Epidemiology and addressable markets

HIV

Globally, the median HIV prevalence among the adult population (aged 15–49 years) was 0.7%. However, the median prevalence was higher among key populations: 2.5% among sex workers. 7.5% among homosexuals. According to UNAIDS, at the end of 2022, there were nearly 39 million people living with HIV worldwide, including nearly 1.5 million children between the ages of 0 and 14. Despite the fact that there has been a drastic reduction (-38%) in the incidence (number of new cases/year) of the virus, there are still 1.5 million new infections. Nearly 29.8 million people are treated with antiretroviral therapy, which would represent a coverage rate of 76%, while 71% of patients have reduced or even suppressed viral loads. In Europe (according to the WHO definition: an enlarged Europe including a number of Eastern European countries), there are 3 million people with HIV, so 63% receive antiviral treatment. The European incidence in 2022 was 180,000 new cases of infection, 0.2 cases/1000 uninfected people. In the United States, the prevalence in 2021 was 1.2 million people with HIV, including nearly 13%. The data reveals that 110 486 HIV diagnoses were made in the European Region in 2022, bringing the total number of diagnoses to 2.4 million. The phenomena of resistance to anti-HIV drug treatments, the priority target of ABL Diagnostics' genotyping techniques, are increasingly significant.

Mycobacterium

Globally, a recent WHO report (https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023/tb-disease-burden/1-3-drug-resistant-tb#:~:text=Globally%2C%20the%20estimated%20proportion%20of,11%E2%80%9323%25)%20in%202022), based on data from 192 countries, shows that 7.5 million people were diagnosed with TB in 2022. This is the highest figure recorded since WHO began monitoring tuberculosis in 1995. This increase is attributed to a good recovery in access to health services and service delivery in many countries. India, Indonesia and the Philippines, which accounted for more than 60% of the global decline in the number of people newly diagnosed with TB in 2020 and 2021, surpassed 2019 levels in 2022. The global incidence is therefore also on the rise, as 10.6 million people contracted tuberculosis in 2022, compared to 10.3 million in 2021. For several years now, we have been witnessing the emergence of tuberculosis bacilli that are insensitive to treatments leading to multidrug-resistant tuberculosis (MDR-TB). This is a real public health crisis. While an estimated 410,000 people contracted multidrug-resistant or rifampicin-resistant tuberculosis (MDR-TB/RR-TB) in 2022, only about two in five people accessed treatment. In addition, we are also witnessing a resurgence of tuberculosis in developed countries, since in 2023, incidence data from Santé Publique France show an increase in tuberculosis cases with 4,728 cases reported in France against 4,217 cases reported in 2022 (an increase of nearly 10.8%). Île-de-France remains the most affected region in metropolitan France with an upward trend in the number of cases between 2022 and 2023.

Hepatic viruses (HBV, HCV, HDV)

It is estimated that approximately 257 million people are living with HBV infection worldwide (HBsAg positivity) of which approximately 15 to 25 million people are infected with HDV, or approximately 5% of chronic hepatitis B virus (HBV) carriers. However, these figures are controversial, and it is likely that the prevalence of HDV infection worldwide is underestimated, due to the lack of routine screening, and the low availability of diagnostic tests. A recent review and meta-analysis, analyzing 182 studies from 61 countries, showed a prevalence of 0.98%, with a prevalence of HDV in HBV carriers of 10.6% (twice as high as previous estimates). Around 3.6 million people in the EU/EEA are chronically infected with hepatitis B virus (HBV), a preventable viral infection that can cause cirrhosis (scarring of the liver) or liver cancer. These particularly impressive data justified the WHO's adoption of a series of recommendations in 2016 for the eradication of viral hepatitis worldwide by 2030. However, this objective will be difficult to achieve, although France, like a number of developed countries, seems to be well on its way to meeting this challenge, which involves speeding up treatments, strengthening diagnosis, whether by rapid orientation test (RDT) or genotyping, in order to adapt treatment. However, the Covid-19 epidemic slowed down a dynamic that had been growing steadily between 2014 and 2017, from 11,500 DAA treatments to 19,250 in 2017. Since 2018, the number has continued to decrease to reach 6,000 treatments in 2021.

Other viruses (herpes, respiratory)

The global prevalence of congenital CMV infection is 0.64% but varies according to socio-economic context. Indeed, while it is around 0.5% to 1% in North America and Europe, it can reach up to 6% in developing countries. Maternal immunity also differs according to socio-economic context (90% for women from lower socio-economic categories compared to 50% for women from higher socio-economic categories). CMV is the leading cause of congenital viral infection worldwide. CMV infections are cosmopolitan and endemic. In France, it is estimated that 50% of the population is seropositive for CMV. Transmission is exclusively human-to-human, with humans being the only reservoir. There are many modes of transmission. There are 2 major peaks of contamination: during early childhood (beginning of life in a community) and between 15-30 years of age (mainly by sexual or saliva transmission). In France, the incidence of CMV infection in pregnant women is 0.6 to 1.4%. The risk of transmission of the virus from mother to child is around 40% (most often by the transplacental

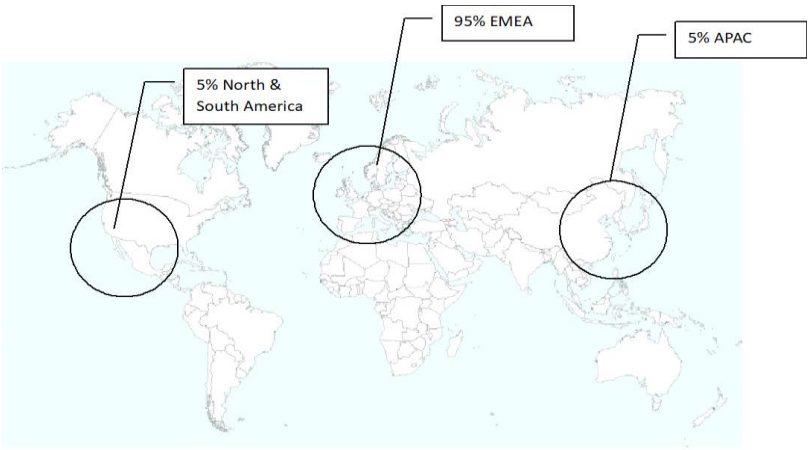
hematogenous route). Currently, CMV infection is the most common opportunistic virus after organ transplantation and the most common congenital viral infection in developed countries (since the release of the rubella vaccine).

Oncology

ABL Diagnostics, using specific human gene sequences, designs primers to detect biomarkers for tumor diagnosis and drug screening. These primers, by their specificity and their amplification by PCR, allow the detection of mutations in "hot spots" identified as tumor biomarkers.

8 A global marketing strategy

ABL Diagnostics currently markets its products using a combination of a direct and indirect model, relying on both its own sales force and a distribution network of some 40 independent regional distributors. Thanks to this, the company covers more than 60 markets worldwide. Today, ABL Diagnostics has sales offices for direct sales.



Source : ABL Dx, IE Finance

At present, direct sales account for around 75% of net sales with activity focused on Western European countries such as France, Germany, Spain, Italy, Benelux, the United Kingdom, Malta, Switzerland, etc., and the company aims to increase this share over the next few years. We believe that this strategy of increasing the share of direct sales should pay off in the long run, as it not only allows the company to build stronger relationships with its customers, but also to gain market share in microbiology and molecular diagnostics, two growing sub-segments. ABL's strategy is obviously to expand its customer portfolio (directly or via its exclusive distributors) but also to expand its activity within each pre-existing customer, by benefiting from a very complete range and by implementing new applications over time with each partner.

Another growing segment for ABL is that of libraries for the SNG: proof of this is the development of the bookstore preparation activity for the SNG, a strategy that has proven its worth, particularly in Lithuania, where ABL responded to a call for tenders with its historical distributor Interlux/Laborama representing an estimated turnover of around €200,000 over two years. This market for generic reagents has a strong and unique commercial potential since it makes it possible to target all laboratories (clinics, universities, research institutes, etc.) performing SNG sequencing, regardless of the platform used, whatever the final application, regardless of the type of sample analyzed. ABL has developed a library preparation kit that is very robust in terms of performance, practicality of use (fast rendering of results) and can position itself on the market with a very competitive offer against the giants of the sector, in particular Illumina.

Of course, we can always use the analogy of the razor/razor blade model to describe the business model adopted by some IVD players, including ABL, but the company does not sell equipment, and therefore razors. On the other hand, it is content to sell consumables at a high margin. Therefore, being "simply" an exclusive supplier of consumables and software solutions should allow ABL to benefit from greater operational leverage and better margins as the company grows. However, there is still the risk of a possible upstream integration of suppliers who develop DNA sequencing instruments. But the barrier to entry can be high because the regulations (CE marking, FDA) and documentation related to routine genetic testing are complex and time-consuming, which suggests high switching costs because customers rarely want to change a proven method (low customer turnover).

8.1 Post-Covid: growth for ABL

ABL Diagnostics' growth is expected to develop along two axes: one purely organic thanks to the gain in market share, the other through the integration of new external skills.

8.1.1 Organic: The Internal Keys

Its direct sales force...

This growing sales network now allows ABL Diagnostics to have a presence in a large number of virology or microbiology laboratories, capable of marketing the entire range of solutions offered. By relying on its internal sales team to make direct sales to its customers (laboratories, clinics, etc.), this distribution channel now represents the bulk of its activity. This sales force, which has about ten in-house employees, can approach its European customers. ABL Diagnostics can also rely on its long-standing customer pool of around 150 laboratories around the world, spread over all continents.

In October 2021, ABL Diagnostics signed a distribution agreement with a renowned strategic partner, giving ABL Diagnostics the possibility of distributing this partner's products, and effectively since February 1, 2022, in the French metropolitan area only. This agreement gives ABL Diagnostics the ability to offer its customers complete end-to-end solutions for genotyping by NGS sequencing, combining both diagnostic kits and the instruments, reagents and services related to this partner's NGS platforms. Microbiology laboratories can access these complementary solutions through different models offered by ABL Diagnostics, either through purchases, rentals or more commonly, through arrangements through which the instruments are installed free of charge and depreciated on the basis of the sale of reagents. In January 2022, ABL Diagnostics signed a collaboration agreement with a recognized foundation, to carry out a clinical evaluation study, led by the WHO, consisting of evaluating the complete *end-to-end* solution proposed by ABL Diagnostics as part of a specific project.

... and indirect: its network of distributors...

These partners have exclusive access to the technologies and products developed by ABL Diagnostics in a given territory and can offer the entire range to all local microbiology laboratories. Among these partners, present in Europe, Latin America, Asia and the Middle East, ABL Diagnostics can count on:

- **GENEPLUS** – In Thailand, Geneplus, a leading distribution company with a team of 30 employees with a strong background in molecular biotechnology and molecular diagnostics, has been representing ABL Diagnostics since February 2022. Also a distributor of brands such as ThermoFisher and MGI, GenePlus has the ability to combine ABL's products with those of these leading sequencing platform suppliers to offer microbiology laboratories complete end-to-end platforms.
- **INTERLUX** – Exclusive distributor of the ABL range in Lithuania for several years, this human-sized company is renowned and respected by laboratories and research institutes in Lithuania and also in the surrounding countries.
- **AB ANALITICA (https://www.abanalitica.com/en/who-we-are/)** – It is a company located in Padua, specialized in molecular biology and which is targeted by ABL to distribute the entire range in Italy from 2024, replacing Technogenetics.
- **PALEX (https://www.palexhealth.com/es-es/home)** – A leading company for the distribution of diagnostic products to Spanish laboratories, which should provide a highly specialized local sales and technical arm by 2024, which would replace the historical partnership with Roche Diagnostics Spain (which has refocused its activities on its own products).
- **EVOLVE LTD** – Evolve, a Maltese company, another historical partner (2015) of ABL Diagnostics, provides tailor-made solutions, ranging from medical laboratory supplies to specialized scientific equipment for pharmaceutical companies.
- **ROCHEM BIOCARE** – Present in Colombia for more than 40 years, Rochem Biocare offers solutions and new technologies for clinical laboratories, technologies for molecular biology, genetics, pathology and life sciences. With its qualified technical service and a group of specialized scientific advisors, it is a long-standing partner of ABL Diagnostics (2016).

With the CE DIV marking of its products and in order to expand its activity and network, ABL Diagnostics intends to integrate new distributors in the coming years.

... to serve its customers...

Among ABL Diagnostics' recurring customers are:

- The ALPHABIO laboratory (Marseille): the laboratory was one of ABL Diagnostics' first customers for genotyping diagnostic tests;
- Some major university laboratories such as the Rouen University Hospital (HIV reference laboratory), the Tours University Hospital (HIV and HCV reference laboratory), the Clermont Ferrand University Hospital, the Amiens University Hospital, the Nancy University Hospital in particular, have entrusted ABL Diagnostics with the performance of genotyping tests on several applications (HIV and SARS-CoV-2).

This short list provides a better understanding of the different types of customers in the field of routine genetic diagnosis, addressed by ABL:

- Private laboratories Whether they are large laboratory chains or somewhat smaller structures, they perform routine diagnostic tests in a wide range of categories, a segment that has grown rapidly in recent years thanks to a higher degree of outsourcing by hospitals. For these structures, the ability to deliver results faster and at a better price is essential. The increased integration (automation, preparation,

sequencing, analysis) of ABL Diagnostics is a step in this direction, constituting a strong value proposition for this group of customers.

- Hospital laboratories that represent the most important segment in the field of genetic diagnostics: structures financed by both the public and private sectors. Here, in-house developed tests (also known as "home brews" or LTD3) are dominant, although interest in NGS-based IVD tests has increased in teaching hospitals in recent years. However, this is a challenging customer segment for players offering new and innovative solutions. For players with a strong value proposition and a solid distribution network, such as ABL, which manage to gain a foothold in large hospital groups, the potential is high.
- public laboratories financed and generally operated by the State and the public authorities (government, municipalities, regions) obey the public procurement code. This tendered customer group is particularly important in the infectious diseases segment. It is worth noting the level of loyalty of ABL Diagnostics' customers is strong, with each contract having an average duration of 15 years.

... with the support of its partners...

Among which we will find:

Source : ABL Diagnostics, Document de référence 2022.

- Prestigious suppliers such as QIAGEN (products for sample preparation), ThermoFisher Scientific (laboratory research and analysis equipment) or Magtivio (preparation of biological samples);
- Recognized medical diagnostic industrial groups and world leaders in genomics (such as Illumina, ThermoFisher Scientific, MGI, etc.);
- Distributors such as Interlux, GenePlus, Roche BioCare, or Evolve (specialized products in microbiology, cell biology, biotechnology, and process control);
- Licensors such as the Laboratoire National de Santé in Luxembourg and the ALPHABIO analysis laboratory (a biomedical laboratory owned by BioGroup).

Building on its internal strengths mentioned above, ABL is currently in a transformation phase and is focused on increasing the share of direct sales by establishing and strengthening its presence in selected markets where it believes it has strong growth prospects. Its sales growth over the past few years (**353%** CAGR for 2019-2022 at the end of the pandemic period) is impressive. However, if we include an extrapolation of 2023 turnover to €4.88 million, this growth still reaches **26%** for the last five years, in line with the growth assessments of the sector of the various marketing firms. We expect this growth to continue in the coming years, thanks to strong market trends and the company's growing product range. In addition, the intensification of the efforts of ABL Diagnostics' direct sales force could potentially increase average selling prices by up to 100% by allowing ABL to appropriate the distributor's margin.

8.1.2 The American Campaign

We believe that ABL should quickly initiate a campaign that we will call American in order to increase its market share in the land of Uncle Sam. Indeed, North America represents 40% of the global diagnostics market and is therefore an important commercial outlet for ABL Diagnostics' tests, both those in the portfolio today and those in development. In 2022, 3,492,034 people were tested for HIV in the USA and 1,958,310 people were diagnosed with cancer. Initially, ABL should target the first 30 to 50 laboratories with a medium to high throughput, because according to the 80/20 rule (20% of laboratories carry out 80% of the analyses). In addition, ABL Diagnostics will develop its direct sales model with a highly experienced sales team represented throughout the country (to be recruited), which should help foster relationships between customers and the sales team, which can be supported by a team of technical and clinical operations experts. We have identified four types of customers for ABL testing that overlap with the list we established above (page 34):

- Large reference laboratories, working with large volumes such as Quest, LabCorp, Sonic Health (between 1500 and 100 tests/day).

- Laboratories in large hospitals with an average throughput of less than 100 tests/day (Kaiser Permanente, Sutter Health, etc.);
- Specialty laboratories (cf. ARUP Labs, Mayo Clinic, etc.) that carry out less than a hundred tests/day.
- Small structures with less than 50 tests/day (Henry Ford Hospital, etc.).
- Prestigious research institutions (cf.: CDC).

8.2 Marketing scenarios and sales models

The state of regulatory registration of the various ABL Diagnostics tests leads us to distinguish between test kits that have received the CE mark and those that are in the process of receiving this regulatory recognition, the first step for reimbursement. CE-marked tests are those that track drug resistance for HIV, tuberculosis or whole genome sequencing for SARS-Cov-2. On the other hand, kits for liver viruses, herpesviruses and respiratory viruses (Influenza, RSV)

8.2.1 HIV: Selling in Europe and the US

ABL Diagnostics aims to continue to market these routine genotyping tests directly through its sales force as well as with its distributors. ABL Diagnostics could ultimately sign a partnership with a major player in IVD. However, for our base case, our assumptions are based on a direct marketing of these tests. By targeting people who have received antiretroviral treatment as a priority, a population that UNAIDS estimated at nearly 29 million out of the 39 million people living with HIV. In the European Union (EU-27), nearly 590,000 people are living with HIV out of the 2.3 million HIV-positive people on the European continent. This distribution shows that the largest proportion of HIV infections are in Eastern Europe, with an incidence of 32.6 HIV-positive people/100,000 people, compared with 10x lower incidences in Western Europe (EU-27: 3.3/100,000). However, resistance is emerging, as highlighted in a latest WHO report[59], which highlights the exponential increase in the number of acquired and transmitted HIV drug resistance among people who have never received antiretroviral therapy, constituting an obstacle to the eradication of the HIV-1 epidemic. The report estimates the prevalence of three- and four-class resistance to be between 5 and 10% in Europe and less than 3% in North America.

EU-26	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
Population	**382 266 370**	**383 145 583**	**384 026 818**	**384 910 080**	**385 795 373**	**386 682 702**	**387 572 072**	**388 463 488**	**389 356 954**	**390 252 475**
HIV prevalence	**955 666**	**957 864**	**960 067**	**962 275**	**964 488**	**966 707**	**968 930**	**971 159**	**973 392**	**975 631**
MDR-HIV Incidence	*7,50%*	*7,50%*	*7,50%*	*7,50%*	*7,50%*	*7,50%*	*7,50%*	*7,50%*	*7,50%*	*7,50%*
HIV incidence	23 000	23 003	23 006	23 009	23 011	23 014	23 017	23 020	23 022	23 025
Undiagnosed pop	124 237	124 522	124 809	125 096	125 383	125 672	125 961	126 251	126 541	126 832
Sum=incidence+unDX	147 237	147 526	147 815	148 104	148 395	148 686	148 978	149 270	149 563	149 857
MDR-HIV pop	11 043	11 064	11 086	11 108	11 130	11 151	11 173	11 195	11 217	11 239
Eligible population	**147 237**	**147 526**	**147 815**	**148 104**	**148 395**	**148 686**	**148 978**	**149 270**	**149 563**	**149 857**
Taux de pénétration	*3,50%*	*4,90%*	*6,86%*	*9,60%*	*13,45%*	*18,82%*	*26,35%*	*26,35%*	*26,35%*	*21,08%*
Tests numbers	5 153	7 229	10 140	14 224	19 953	27 988	39 261	39 338	39 415	31 594
CA HIV	3 182 161	4 463 754	6 261 503	8 783 291	12 320 723	17 282 851	24 243 474	24 291 065	24 338 764	19 509 258
CA total	**3,18**	**4,46**	**6,26**	**8,78**	**12,32**	**17,28**	**24,24**	**24,29**	**24,34**	**19,51**

Amérique du nord	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
Population USA	334 058 400	334 826 734	335 596 835	336 368 708	337 142 356	337 917 784	338 694 994	339 473 993	340 254 783	341 037 369
HIV Prevalence	***1 314 722***	***1 353 139***	***1 391 644***	***1 430 237***	***1 468 920***	***1 507 691***	***1 546 552***	***1 585 502***	***1 624 541***	***1 663 670***
HIV Incidence	38 417	38 505	38 594	38 682	38 771	38 861	38 950	39 040	39 129	39 219
Undiagnosed pop	170 914	175 908	180 914	185 931	190 960	196 000	201 052	206 115	211 190	216 277
Sum=incidence+unDX	209 331	214 413	219 507	224 613	229 731	234 860	240 002	245 155	250 320	255 496
MDR-HIV pop	15 700	16 081	16 463	16 846	17 230	17 615	18 000	18 387	18 774	19 162
Eligible population	**225 030**	**230 494**	**235 970**	**241 459**	**246 961**	**252 475**	**258 002**	**263 541**	**269 094**	**274 659**
Diagnosable patients	*175 524*	*179 785*	*184 057*	*188 338*	*192 629*	*196 930*	*201 241*	*205 562*	*209 893*	*214 234*
Pénétration rate			*1,20%*	*2,40%*	*4,80%*	*9,60%*	*10,00%*	*10,00%*	*10,00%*	*10,00%*
Tests numbers		0	2 209	4 520	9 246	18 905	20 124	20 556	20 989	21 423
CA HIV		0,0	1 363 861,6	2 791 172,5	5 709 535,5	11 674 037,0	12 426 655,6	12 693 468,3	12 960 894,7	13 228 936,1
CA USA total		**0,00**	**1,36**	**2,79**	**5,71**	**11,67**	**12,43**	**12,69**	**12,96**	**13,23**

Source : ABL Diagnostics, Estimations IE Finance

The positioning of ABL Diagnostics' kits for the study of HIV drug resistance, CE marked, ensures an advantageous position, particularly in the face of competition from ThermoFisher in SANGER sequencing and Vela Diagnostics in NGS. Also, we believe that ABL is able to gain substantial market share in both Europe and the United States. However, we believe that the attack on the US market will only be possible after a regulatory stage.

8.2.2 Drug-resistant tuberculosis: meeting the WHO.

For several years, there has been a resurgence of tuberculin infections in regions such as Europe and the USA. Despite a downward trend in terms of prevalence, the current data do not meet the WHO's public health requirements, particularly in the interruption of transmission (identification of carriers of the germ) and development for infected people. Thus, in 2021, there were nearly 166,000 new cases and relapses in "enlarged" Europe, while at the same time, "only" in 2021, 33,520 cases of tuberculosis were reported in the EU.

[59] https://www.who.int/publications/i/item/9789240038608

EU-26	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
Population	**382 266 370**	**383 145 583**	**384 026 818**	**384 910 080**	**385 795 373**	**386 682 702**	**387 572 072**	**388 463 488**	**389 356 954**	**390 252 475**
TB prevalence	**36 346**	**36 429**	**36 513**	**36 597**	**36 681**	**36 766**	**36 850**	**36 935**	**37 020**	**37 105**
TB Nb cases/yr	9 939	9 962	9 985	10 008	10 031	10 054	10 077	10 100	10 123	10 147
MDR-TB Nb cases/yr	*775*	*777*	*779*	*781*	*782*	*784*	*786*	*788*	*790*	*792*
XDR-TB Nb cases/Yr	116	116	116	117	117	117	117	118	118	118
Co-Infection HIV-TB	13 436	13 436	13 436	13 436	13 436	13 436	13 436	13 436	13 436	13 436
TB developed	1 146 799	1 149 437	1 152 080	1 154 730	1 157 386	1 160 048	1 162 716	1 165 390	1 168 071	1 170 757
Eligible population	**1 171 065**	**1 173 728**	**1 176 396**	**1 179 071**	**1 181 752**	**1 184 439**	**1 187 133**	**1 189 832**	**1 192 538**	**1 195 250**
Taux de pénétration	*0,50%*	*1,00%*	*2,00%*	*4,00%*	*8,00%*	*16,00%*	*16,00%*	*16,00%*	*16,00%*	*12,80%*
Tests numbers	5 855	11 737	23 528	47 163	94 540	189 510	189 941	190 373	190 806	152 992
CA ALS	1 182 776	2 370 930	4 752 641	9 526 895	19 097 115	38 281 077	38 368 125	38 455 373	38 542 821	30 904 377
CA total	**1,18**	**2,37**	**4,75**	**9,53**	**19,10**	**38,28**	**38,37**	**38,46**	**38,54**	**30,90**

USA	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
Population USA	334 058 400	334 826 734	335 596 835	336 368 708	337 142 356	337 917 784	338 694 994	339 473 993	340 254 783	341 037 369
TB Prevalence	***8 351***	***8 371***	***8 390***	***8 409***	***8 429***	***8 448***	***8 467***	***8 487***	***8 506***	***8 526***
TB Nb cases/yr	8 351	8 371	8 390	8 409	8 429	8 448	8 467	8 487	8 506	8 526
MDR-TB Nb cases/yr	678	679	681	682	684	685	687	689	690	692
XDR-TB Nb cases/Yr	101	101	102	102	102	102	103	103	103	103
Co-Infection HIV-TB	49 107	49 220	49 333	49 446	49 560	49 674	49 788	49 903	50 017	50 132
TB developed	1 002 175	1 004 480	1 006 791	1 009 106	1 011 427	1 013 753	1 016 085	1 018 422	1 020 764	1 023 112
Eligible population	**1 060 412**	**1 062 851**	**1 065 295**	**1 067 746**	**1 070 201**	**1 072 663**	**1 075 130**	**1 077 603**	**1 080 081**	**1 082 566**
Taux de pénétration		*0,00%*	*0,25%*	*0,50%*	*1,00%*	*2,00%*	*4,00%*	*4,80%*	*4,80%*	*4,80%*
Test Numbers		0	2 663	5 339	10 702	21 453	43 005	51 725	51 844	51 963
CA ALS		0,0	537 974,2	1 078 423,1	2 161 807,0	4 333 558,3	8 687 051,0	10 448 437,4	10 472 468,8	10 496 555,5
CA USA total		**0,00**	**0,54**	**1,08**	**2,16**	**4,33**	**8,69**	**10,45**	**10,47**	**10,50**

Source : ABL Diagnostics, Estimations IE Finance

Treatment success rates for both the EU and the WHO wider European Region (WHO) at 73.4% and 57.2% respectively, remain well below the targets. The situation is similar when we look at new cases and relapses, since 71.7% of these obtained a positive therapeutic result at 12 months in 2021. On the other hand, for resistant tuberculosis, the success rates of treatment fall significantly. The treatment success rate at 24 months for RR/MDR TB was 51.7%; for drug-resistant pre-extensive tuberculosis (XDR), it was 17.0%. The treatment success rate at 36 months for XDR-TB was 66.7%.

8.2.3 SNG: Preparing Libraries

ABL Diagnostics is present in the SNG value chain, offering library preparations in a "vendor-agnostic" approach, so they do not depend on equipment. This allows the kits offered to be used on a large number of sequencers, including those offered by the most important suppliers (Illumina, Agilent, Roche, Pacific Bio...). In addition, this market for preparing libraries for the SNG is now "flourishing". An encouraging sign is that there have been countless market studies relating to this segment of SNG. Indeed, this step, as we mentioned above, is essential for the smooth running of the process, but it is also a guarantee of quality for the results obtained. Although this activity currently represents only a relatively small share of total sales, we believe, especially after the Lithuanian contract, that this should be one of the promising segments for ABL Diagnostics' activity. In its manufacturing process, the company acquires raw materials from selected suppliers that it has evaluated on the basis of certain criteria. It performs quality control and manufacturing of critical components in-house. This ensures the high quality of its finished products.

	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
Global SNG market (Nova One Advisor)	***12 498***	***16 998***	***23 117***	***31 439***	***42 757***	***58 150***	***79 084***	***107 554***	***146 274***	***198 932***
Global NGS Library Prep (Nova One Advisor)	*1 618*	*1 832*	*2 073*	*2 346*	*2 656*	*3 006*	*3 402*	*3 850*	*4 358*	*4 932*
EU-26										
European NGS Sample Prep	*324*	*366*	*415*	*469*	*531*	*601*	*680*	*770*	*872*	*986*
Taux de pénétration	*0,01%*	*0,01%*	*0,03%*	*0,04%*	*0,05%*	*0,07%*	*0,09%*	*0,12%*	*0,16%*	*0,20%*
Sales	0,02	0,05	0,13	0,20	0,29	0,43	0,63	0,93	1,37	2,01
Total Sales	**0,02**	**0,05**	**0,13**	**0,20**	**0,29**	**0,43**	**0,63**	**0,93**	**1,37**	**2,01**
Total Sales EU	0,02	0,05	0,13	0,20	0,29	0,43	0,63	0,93	1,37	2,01

USA + Canada	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
US SNG market (Nova One Advisor)	***4 499***	***6 119***	***8 322***	***11 318***	***15 393***	***20 934***	***28 470***	***38 719***	***52 658***	***71 616***
USA	*3 150*	*4 283*	*5 825*	*7 923*	*10 775*	*14 654*	*19 929*	*27 104*	*36 861*	*50 131*
Canada	*1 350*	*1 836*	*2 497*	*3 395*	*4 618*	*6 280*	*8 541*	*11 616*	*15 798*	*21 485*
US SNG Library prep kit Market (bn)	**388**	**440**	**498**	**563**	**637**	**721**	**816**	**924**	**1 046**	**1 184**
Taux de pénétration	*0,00%*	*0,00%*	*0,00%*	*0,06%*	*0,08%*	*0,12%*	*0,19%*	*0,24%*	*0,31%*	*0,41%*
Sales	0,00	0,00	0,00	0,31	0,53	0,89	1,52	2,23	3,28	4,83
Total Sales	**0,00**	**0,00**	**0,00**	**0,31**	**0,53**	**0,89**	**1,52**	**2,23**	**3,28**	**4,83**
Total Sales North America	0,00	0,00	0,00	0,31	0,53	0,89	1,52	2,23	3,28	4,83

Asie-Pacifique	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
Asie-Pacific SNG market (Nova One Advisor)	***3 750***	***5 099***	***6 935***	***9 432***	***12 827***	***17 445***	***23 725***	***32 266***	***43 882***	***59 680***
Chine	*2 625*	*3 570*	*4 855*	*6 602*	*8 979*	*12 211*	*16 608*	*22 586*	*30 717*	*41 776*
Autres	*1 125*	*1 530*	*2 081*	*2 830*	*3 848*	*5 233*	*7 118*	*9 680*	*13 165*	*17 904*
Asia-Pacific SNG Library prep kit Market (bn)	**356**	**403**	**456**	**516**	**584**	**661**	**748**	**847**	**959**	**1 085**
Taux de pénétration	*0,00%*	*0,00%*	*0,00%*	*0,06%*	*0,08%*	*0,12%*	*0,19%*	*0,24%*	*0,31%*	*0,41%*
Sales	0,00	0,00	0,00	0,28	0,48	0,82	1,39	2,04	3,01	4,43
Total Sales	**0,00**	**0,00**	**0,00**	**0,28**	**0,48**	**0,82**	**1,39**	**2,04**	**3,01**	**4,43**
Total Sales Asie-Pacific	0,00	0,00	0,00	0,28	0,48	0,82	1,39	2,04	3,01	4,43
CA total	**0,02**	**0,05**	**0,13**	**0,79**	**1,30**	**2,14**	**3,54**	**5,20**	**7,65**	**11,26**

Source : ABL Diagnostics, Estimations IE Finance

In our library sales model for the SNG, ABL Diagnostics initially focuses on the European market according to its traditional model (direct and indirect sales that we have not individualized in the table above). The ramp-up is relatively small, because ABL Diagnostics will need the ability to negotiate market shares to the detriment of SNG

equipment manufacturers who also market library preparation kits. We also believe that a partnership agreement with MGI Tech should make it easier for it to enter the Chinese market. Indeed, MGI Tech is a Chinese company that develops and offers a range of products and technologies for the genetic sequencing, genotyping and gene expression, and proteomics markets. In addition, MGI, by launching in 2022, its very high-throughput sequencer DNBSEQ-T20x2, which can produce up to 50,000 whole genome sequences (WGS) per year for 30x human genomes, makes the NGS more accessible for laboratories (close to $100/sequencing).

8.2.4 NADIS,® a specialized electronic medical record

With NADIS,® ABL Diagnostics offers software dedicated to the management of patients with infectious diseases (HIV, liver viruses, etc.). This tool allows for the daily monitoring of patients, also integrating sections for doctors, nurses, and pharmacists. In addition to follow-up, NADIS® makes it possible to prescribe medication. This is a form of electronic medical record for a specialty, since all the information presents. The revenue generated through the NADIS® activity corresponds to the marketing of the software. Thanks to the subscriptions generated, it is a source of recurring revenue. Used in more than 200 French hospitals and French-speaking hospitals in Africa, ABL Diagnostics has developed gateways with a large number of SILs (Laboratory Information Services) allowing the data produced to be automatically uploaded to the patient file. The level of customer satisfaction is high and results in a high recurrence rate. In June 2023, the AP-HP (Assistance Publique-Hôpitaux de Paris) renewed its contract with ABL Diagnostics for the use of NADIS® for another four years. In addition, ABL has also developed an extension of NADIS,® in an application format for patients, MyNadis®, which allows direct use of the functionalities by the patient. MyNadis® is perfectly in line with the current trend of the patient himself "taking control" of the patient journey. We believe that NADIS® can and should continue to increase its market share both in France and in Europe, as the Electronic Health Record market is currently growing rapidly with annual growth rates ranging from 4.1% to 8.2% for the most optimistic of marketing research firms, from $18.82 billion to $48.3 billion. To do this, after an English translation, ABL Diagnostics will deploy NADIS® and MyNadis® internationally with the objective of exceeding the current 9% of turnover.

France		**2024**	**2025**	**2026**	**2027**	**2028**	**2029**	**2030**	**2031**	**2032**	**2033**
population		**65 930 912**	**66 260 566**	**66 591 869**	**66 924 828**	**67 259 453**	**67 595 750**	**67 933 729**	**68 273 397**	**68 614 764**	**68 957 838**
Health Infrastructures nb		**2 491**	**2 399**	**2 310**	**2 225**	**2 142**	**2 063**	**1 987**	**1 913**	**1 843**	**1 774**
	Public Hospital	*1 121*	*1 080*	*1 040*	*1 001*	*964*	*929*	*894*	*861*	*829*	*799*
	Private Hopitals	*777*	*748*	*720*	*694*	*668*	*643*	*620*	*597*	*575*	*553*
	Others structures	*307*	*296*	*285*	*274*	*264*	*254*	*245*	*236*	*227*	*219*
Hospital equiped		192	196	200	204	208	212	216	221	225	229
CeGIDD equiped		25	26	26	27	27	28	28	29	29	30
Penetration rate		*8,71%*	*9,23%*	*9,77%*	*10,35%*	*10,96%*	*11,61%*	*12,30%*	*13,03%*	*13,80%*	*14,62%*
Total equiped		217	221	226	230	235	240	244	249	254	259
Nadis Sales		599 771,35	611 766,78	624 002,12	636 482,16	649 211,80	662 196,04	675 439,96	688 948,76	702 727,73	716 782,29
Total Sales		**0,60**	**0,61**	**0,62**	**0,64**	**0,65**	**0,66**	**0,68**	**0,69**	**0,70**	**0,72**
evolution (%)			*2,0%*	*2,0%*	*2,0%*	*2,0%*	*2,0%*	*2,0%*	*2,0%*	*2,0%*	*2,0%*

EU-26		**2024**	**2025**	**2026**	**2027**	**2028**	**2029**	**2030**	**2031**	**2032**	**2033**
Population		**382 266 370**	**383 145 583**	**384 026 818**	**384 910 080**	**385 795 373**	**386 682 702**	**387 572 072**	**388 463 488**	**389 356 954**	**390 252 475**
Hospital beds		**2 331 092**	**2 326 430**	**2 321 777**	**2 317 134**	**2 312 499**	**2 307 874**	**2 303 259**	**2 298 652**	**2 294 055**	**2 289 467**
Health Infrastructures nb		**17 015**	**16 981**	**16 947**	**16 913**	**16 880**	**16 846**	**16 812**	**16 778**	**16 745**	**16 711**
	Public Hospital	*6 881*	*6 627*	*6 381*	*6 145*	*5 918*	*5 699*	*5 488*	*5 285*	*5 090*	*4 901*
	Private Hopitals	*4 767*	*4 591*	*4 421*	*4 257*	*4 100*	*3 948*	*3 802*	*3 661*	*3 526*	*3 395*
	Others structures	*1 885*	*1 816*	*1 749*	*1 684*	*1 622*	*1 562*	*1 504*	*1 448*	*1 395*	*1 343*
Penetration rate		*0,03%*	*0,05%*	*0,10%*	*0,20%*	*0,40%*	*0,80%*	*1,60%*	*2,00%*	*2,50%*	*3,13%*
Hospital equiped		4	8	17	34	68	135	269	336	419	522
Nadis Sales		11 757,23	23 467,42	46 840,98	93 494,60	186 615,21	372 483,97	743 478,00	927 488,80	1 157 042,28	1 443 410,25
EU Total Sales			**0,02**	**0,05**	**0,09**	**0,19**	**0,37**	**0,74**	**0,93**	**1,16**	**1,44**
evolution (%)			*#DIV/0!*	*99,6%*	*99,6%*	*99,6%*	*99,6%*	*99,6%*	*24,8%*	*24,8%*	*24,8%*
Total Sales EU+FR		0,60	0,64	0,67	0,73	0,84	1,03	1,42	1,62	1,86	2,16

Source : ABL Diagnostics, Estimations IE Finance

8.2.5 Other viruses

8.2.5.1 Hepatic viruses

While therapeutic and technological progress has greatly improved the management of viro-induced hepatitis, viral evasion of treatments remains a public health reality. These increasingly common escapes are the result of prolonged exposure to antivirals, which, by inducing selection pressure on wild strains of viruses, allow the emergence of resistance mutations. According to the WHO, the resurgence of viral hepatitis cases with 1.2 million cases of hepatitis B and nearly one million new cases of hepatitis C in 2022, reflects a difficult context in the fight against viral hepatitis, with high infection rates. The WHO estimates that there are 250 to 300 million chronic HBV carriers worldwide.

8.2.5.2 Herpesvirus

The global prevalence of congenital CMV infection is 0.64%, but often varies according to socioeconomic context. Indeed, while it is around 0.5-1% in North America and Europe, it can reach up to 6% in developing countries. CMV is the leading cause of congenital viral infection worldwide. It is estimated that 50% of the population in France is HIV-positive for CMV. Transmission is exclusively human-to-human, with humans being the only reservoir. However, CMV currently poses a major public health problem in immunocompromised individuals, because the morbidity associated with it, particularly in the context of organ transplants, remains an unmet medical need. The incidence of these post-transplant complications is significant 70% in the three months after

surgery (in 2010). In addition, the occurrence of drug resistance (around 10%) is also an additional problem, particularly with regard to *ganciclovir*, *foscavir* and/or *cidofovir*. The causes of the emergence of this resistance are multiple: prolonged exposure to antiviral treatments, the use of a suboptimal dose of antiviral or the existence of immunosuppression. It is estimated that nearly 50% of non-responses to treatments are due to significant virological resistance which, by inducing selection pressure on wild strains, leads to the emergence of resistant strains.

8.2.6 Oncology

In 2020, the number of new cases of cancer amounted to 2.7 million cases in Europe (EU-27), of which 1.4 million affected men (54%) and 1.2 million women. In the face of this increase, the need for relevant diagnostics is also expected to increase. Indeed, we are witnessing a real shift in diagnostic practice, which today focuses on communicating information independent of the stage of development of the tumor mass. But the contribution of molecular diagnostics, which is developing rapidly, is to identify molecular events at the initiation of cancerization phenomena to allow the rapid emergence of precision medicine. One of the avenues is to decipher the point, somatic mutations of tumor cells in order to determine, for example, their sensitivity to this or that chemotherapy. Research in genomic characterization is progressing rapidly. Thus, the TCGA (*Genomic Atlas of Cancer*) has gone from 300 initiator genes identified in 2015 to nearly 507 genes today. In 2015, 57% of the tumours analysed had a potentially actionable oncogenic event.

EU-26	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
Population	**382 266 370**	**383 145 583**	**384 026 818**	**384 910 080**	**385 795 373**	**386 682 702**	**387 572 072**	**388 463 488**	**389 356 954**	**390 252 475**
Cancer Incidence	**2 776 398**	**2 795 832**	**2 815 403**	**2 835 111**	**2 854 957**	**2 874 941**	**2 895 066**	**2 915 331**	**2 935 739**	**2 956 289**
Cancer prevalence	**13 690 328**	**16 486 160**	**19 301 563**	**22 136 674**	**24 991 631**	**27 866 572**	**30 761 638**	**33 676 970**	**36 612 708**	**39 568 997**
genetic testiong rate incidence	*6,80%*	*6,80%*	*6,80%*	*6,80%*	*6,80%*	*6,80%*	*6,80%*	*6,80%*	*6,80%*	*6,80%*
Eligible tests/yr	*113 916*	*114 713*	*115 516*	*116 325*	*117 139*	*117 959*	*118 785*	*119 616*	*120 453*	*121 297*
Eligibled tests	85 437	86 035	86 637	87 243	87 854	88 469	89 088	89 712	90 340	90 972
Taux de pénétration	*0,20%*	*0,40%*	*0,80%*	*1,20%*	*1,80%*	*2,70%*	*4,05%*	*6,08%*	*7,59%*	*9,49%*
Tests realized	171	344	693	1 047	1 581	2 389	3 608	5 450	6 860	8 635
CA tests oncol	126 942	255 661	514 901	777 758	1 174 803	1 774 540	2 680 443	4 048 810	5 096 439	6 415 143
CA total	**0,13**	**0,26**	**0,51**	**0,78**	**1,17**	**1,77**	**2,68**	**4,05**	**5,10**	**6,42**
evolution (%)	*67,8%*	*101,4%*	*101,4%*	*51,1%*	*51,1%*	*51,1%*	*51,1%*	*51,1%*	*25,9%*	*25,9%*
CA total EU	0,19	0,35	0,86	1,38	2,19	3,46	5,47	8,62	11,29	14,77

Amérique du nord	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
Population USA	**334 058 400**	**334 826 734**	**335 596 835**	**336 368 708**	**337 142 356**	**337 917 784**	**338 694 994**	**339 473 993**	**340 254 783**	**341 037 369**
Cancer Incidence	***2 001 140***	***2 005 743***	***2 010 356***	***2 014 980***	***2 019 614***	***2 024 259***	***2 028 915***	***2 033 582***	***2 038 259***	***2 042 947***
genetic testiong rate incidence	*6,80%*	*6,80%*	*6,80%*	*6,80%*	*6,80%*	*6,80%*	*6,80%*	*6,80%*	*6,80%*	*6,80%*
Eligible tests/yr	*82 107*	*82 296*	*82 485*	*82 675*	*82 865*	*83 055*	*83 246*	*83 438*	*83 630*	*83 822*
Eligibled tests	61 580	61 722	61 864	62 006	62 149	62 292	62 435	62 578	62 722	62 867
Taux de pénétration		*0,20%*	*0,12%*	*0,20%*	*0,40%*	*0,80%*	*1,20%*	*1,80%*	*2,70%*	*4,05%*
Tested realized		123	74	124	249	498	749	1 126	1 694	2 546
CA tests oncol		91 706,1	55 150,2	92 128,5	184 680,7	370 210,9	556 593,6	836 810,7	1 258 103,1	1 891 495,0
CA USA total		**0,09**	**0,06**	**0,09**	**0,18**	**0,37**	**0,56**	**0,84**	**1,26**	**1,89**
CA total Amerique du Nord	**0,00**	**0,09**	**0,06**	**0,09**	**0,18**	**0,37**	**0,56**	**0,84**	**1,26**	**1,89**
CA total	**0,19**	**0,44**	**0,92**	**1,47**	**2,37**	**3,83**	**6,03**	**9,46**	**12,55**	**16,66**

ABL Diagnostics addresses the oncology genotyping market with a panel of genes representing hot spots on which the company searches in RUO for somatic mutations associated with cancer. The advantage of such a multiplexed approach is to be able to study several samples for several cancers such as melanoma and lung, colon, breast, ovarian and prostate cancer.

9 Financial elements and performance

ABL Diagnostics has certainly had to suffer from the slowdown in demand for Covid tests like the entire IVD sector, but unlike many of its competitors, it has been able to generate growth with its proprietary products, but also with new products and services (NADIS),® which allow it to position itself at several stages of the health care journey (diagnostics, data collection, analysis, interpretation, storage).

9.1 A good 2023 financial year...

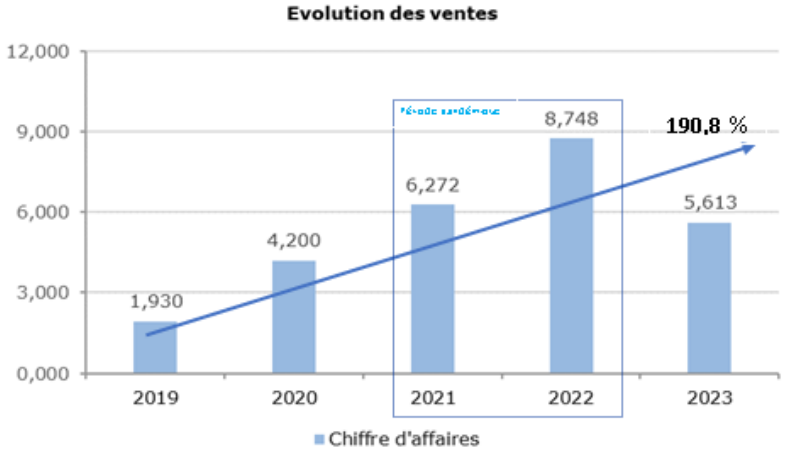
ABL Diagnostics' final financial statements for the 2023 financial year show a turnover of €5.61 million corresponding to the sale of diagnostic kits. Revenue, 68.2% of which was generated by the sale of diagnostic kits and 31.7% by service (concession of the use of NADIS® software and distributor licenses).

	2019	2020	2021	2022	2023
Chiffre d'affaires	**1,930**	**4,200**	**6,272**	**8,748**	**5,613**
Subventions Exploitation	0,000	0,000	0,000	0,013	0,069
Autres Produits	0,006	0,033	0,559	0,006	0,007
Produits exploitation	**1,937**	**4,233**	**6,830**	**9,394**	**7,694**
Achats consommés	0,194	1,454	1,70	1,04	1,31
Marge brute	**1,742**	**2,779**	**5,128**	**8,354**	**6,384**
Impôts et taxes	0,007	0,026	0,045	0,042	0,005
Salaires et Traitements	0,594	0,852	1,287	0,942	1,075
Charges sociales	0,000	0,000	0,000	0,389	0,383
Autres charges externes	1,403	1,804	2,303	5,227	3,761
Autres produits et charges d'exploitation	0,000	0,000	0,000	0,000	0,000
EBITDA	**-0,427**	**-0,037**	**1,360**	**1,643**	**0,498**
Dépréciation et amortissements	0,359	1,018	0,788	1,584	1,155
EBIT	**-0,452**	**0,440**	**1,402**	**0,059**	**-0,657**
Résultat financier	-0,016	-0,012	0,021	0,018	-0,014
Résultat exceptionnel	0,322	0,153	-0,174	0,413	0,047
Résultat courant avant impôts	**-0,145**	**0,581**	**1,249**	**0,490**	**-0,624**
Impôts	-0,350	-0,388	-0,272	-0,615	-0,678
Résultat Net	**0,205**	**0,970**	**1,521**	**1,106**	**0,055**
Résultat Net part du groupe	**0,205**	**0,970**	**1,521**	**1,106**	**0,055**
TN			3,149	1,01	2,01
Résultat dilué/Action	**0,013**	**0,060**	**0,094**	**0,069**	**0,003**
Nombre moyen pondéré d'actions	16,11	16,11	16,11	16,11	16,11

Although not yet communicated, we believe that the geographical breakdown of this turnover should follow that of previous years (as in 2022, exports of tests and services at 69.3% of turnover and sales in France at 30.7%). Operating expenses amounted to €8.78 million, which were offset by operating income, which amounted to €8.15 million. The cost of purchases for sales was €1.31 million associated with a positive change in inventories of €0.221 million. The gross margin is relatively stable and the gross margin rate hovers around 83%, reflecting the work carried out by ABL Diagnostics to retain suppliers and subcontractors. Other purchases and external expenses were also well controlled, down to €3.76 million, reflecting the increased level of integration of the company's value chain. Personnel costs, which stand at €1.46 million, are also under control, with stability over the last few years. The result was an EBITDA of €0.49 million and an increase in operating income of €-0.65 million. Thanks to a slightly negative financial result of -€0.014 million, an exceptional result of €0.047 million, and a tax credit of €0.678 million, the positive net result was €0.05 million. As of December 31, 2022, the company ended FY23 with a cash position of €2.01 million.

9.2 … marked by continued growth in turnover…

Over the last few years, ABL Diagnostics' sales have grown strongly by more than 190% over the last five years, despite the anticipated significant decline in molecular tests specific to the SARS-CoV-2 pathogen, observed throughout the industry. Over this period, there have been increasing sales of HIV tests, as the number of active customers for HIV genotyping has almost quadrupled over the last four years (from 26 in 2020 to 84 in 2023), as have test orders, which have also increased by a factor of 4 (110 in 2020 to 405 in 2023), reflecting the interest



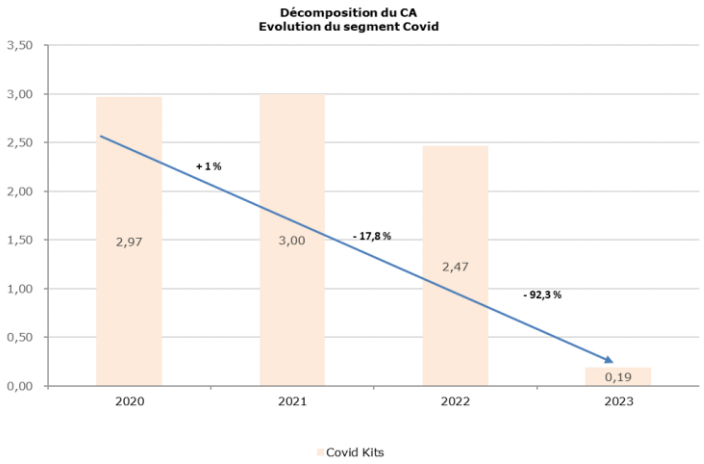
Source : ABL Diagnostics, Estimations IE Finance.

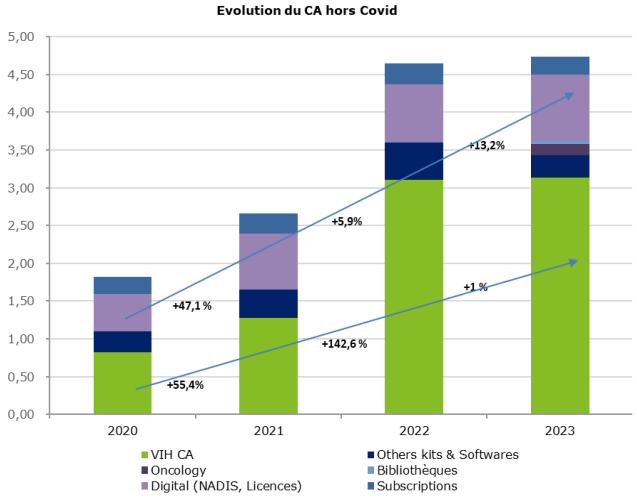
of the sector in ABL Diagnostics' proposal. Moreover, everything suggests that this trend should continue in the coming years.
In addition, there is also a greater demand for genotyping tests for liver viruses as well as tests for herpesviruses and respiratory syndromes, which are long-term and sustainable markets.

9.3 … despite a drop in Covid tests…

Several Covid customers are currently migrating and testing or have started purchasing DeepChek® kits for other indications. Based on the data from FY23, the decline in Covid test sales is even more pronounced, reaching -92.3%. This decline was offset by ABL Diagnostics' proprietary products such as HIV tests and tests for other viruses. The slowdown in Covid tests began during the pandemic period, since between 2020 and 2021, the growth in sales of Covid kits was only one percent, and between 2021 and 2023, this erosion continued. A situation that shows that "there is life before, during and after Covid", especially when you have an in-house innovation and development activity for proprietary products (HIV kits, other viruses, software), which fortunately ABL Diagnostics has, allowing it to generate growth.

In 2023, the trend already observed during the pandemic period was confirmed, namely a significant increase in HIV tests concomitantly with a more than significant reduction in molecular tests for SARS-Cov-2, a phenomenon observed for the entire IVD industry. Thus, between 2021 and 2022, HIV tests increased by 142% and were maintained during the 2023 financial year. Sales of non-Covid products represented 96.5% of sales in 2023 in the 2023 financial year.





Source : ABL Diagnostics, Estimations IE Finance.

9.4 … and thanks to new growth drivers

ABL Diagnostics has shown that it has the ability to develop outside of Covid tests and that outside of "the pandemic parenthesis", its ability to seek sustainable growth with proprietary products resulting from its research and development. In addition, with its integration allowing it to manufacture and market alone or/and with its distributors, while responding positively to its customers' requests, it shows that ABL has a number of assets to consolidate its position in the IVD. With a continued focus on the international market, we believe that sales will grow with the strengthening of the presence in the EU, new products (libraries for SNGs) and as products are approved in the United States. ABL Diagnostics is expected to maintain its strategy of focusing on high-volume customer groups such as high-throughput laboratories, multi-hospital groups, private pathology chains and government programs.

We believe that ABL Diagnostics has an attractive financial profile, showing continuous growth for several years with particularly attractive gross margin rates. Due to its presence in a large number of markets (around sixty), ABL Diagnostics has become a recognized brand. We believe that the next goals of the company will be:

- Improve its position on the market (cf. the US market);
- To increase its activities (cf. the life sciences activity with the preparation of libraries for the SNG;
- To modify its marketing mix not only in geographical terms (USA) but also in commercial terms (increase the share of direct sales according to the markets);

As can be seen in the following projections:

Ventes par segment	2024e	2025e	2026e	2027e	2028e	2029e	2030e	2031e	2032e	2033e
VIH	**3,18**	**3,99**	**6,06**	**8,40**	**11,73**	**15,94**	**21,39**	**28,17**	**36,89**	**47,70**
% of net sales	*50,49%*	*46,78%*	*47,56%*	*47,57%*	*47,98%*	*47,97%*	*47,00%*	*46,14%*	*47,24%*	*46,96%*
TB	**0,70**	**0,85**	**1,49**	**1,91**	**2,57**	**3,63**	**5,20**	**7,16**	**9,82**	**13,81**
% of net sales	11,15%	9,92%	11,66%	10,84%	10,50%	10,94%	11,43%	11,73%	12,57%	13,59%
Others Virus (hépatiques, Herpesvirus…)	**0,90**	**1,71**	**2,27**	**3,18**	**4,44**	**5,43**	**6,66**	**8,16**	**9,50**	**10,84**
% of net sales	*14,25%*	*20,05%*	*17,81%*	*18,02%*	*18,16%*	*16,34%*	*14,62%*	*13,37%*	*12,17%*	*10,67%*
COVID	**0,71**	**0,86**	**1,21**	**1,23**	**1,25**	**1,23**	**1,21**	**1,19**	**1,17**	**1,15**
% of net sales	50,49%	46,78%	47,56%	47,57%	47,98%	47,97%	47,00%	46,14%	47,24%	46,96%
Oncology	**0,19**	**0,44**	**0,92**	**1,47**	**2,37**	**3,83**	**6,03**	**9,46**	**12,55**	**16,66**
% of net sales	*3,00%*	*5,17%*	*7,21%*	*8,31%*	*9,70%*	*11,54%*	*13,24%*	*15,49%*	*16,07%*	*16,40%*
Life Science (Bibliothèques)	**0,60**	**0,64**	**0,67**	**0,73**	**0,84**	**1,03**	**1,42**	**1,62**	**1,86**	**2,16**
% of net sales	9,52%	7,46%	5,27%	4,13%	3,42%	3,11%	3,12%	2,65%	2,38%	2,13%
Digital (NADIS, Licences)	**0,60**	**0,64**	**0,67**	**0,73**	**0,84**	**1,03**	**1,42**	**1,62**	**1,86**	**2,16**
% of net sales	*9,52%*	*7,46%*	*5,27%*	*4,13%*	*3,42%*	*3,11%*	*3,12%*	*2,65%*	*2,38%*	*2,13%*
Sales by sales channels										
Direct sales	**4,73**	**6,65**	**10,19**	**14,49**	**20,29**	**27,58**	**38,23**	**51,90**	**66,37**	**86,34**
% of net sales	75,00%	78,00%	80,00%	82,00%	83,00%	83,00%	84,00%	85,00%	85,00%	85,00%
Distributor sales	**1,58**	**1,87**	**2,55**	**3,18**	**4,16**	**5,65**	**7,28**	**9,16**	**11,71**	**15,24**
% of net sales	25,00%	22,00%	20,00%	18,00%	17,00%	17,00%	16,00%	15,00%	15,00%	15,00%
Sales by geography										
EMEA	**5,67**	**7,50**	**10,32**	**13,96**	**19,06**	**24,92**	**33,22**	**43,97**	**53,88**	**67,04**
% of net sales	90,00%	88,00%	81,00%	79,00%	78,00%	75,00%	73,00%	72,00%	69,00%	66,00%
North & South America	**0,32**	**0,68**	**1,53**	**2,65**	**4,40**	**6,65**	**9,56**	**13,43**	**18,74**	**25,39**
% of net sales	5,00%	8,00%	12,00%	15,00%	18,00%	20,00%	21,00%	22,00%	24,00%	25,00%
APAC	**0,32**	**0,34**	**0,89**	**1,06**	**0,98**	**1,66**	**2,73**	**3,66**	**5,47**	**9,14**
% of net sales	5,00%	4,00%	7,00%	6,00%	4,00%	5,00%	6,00%	6,00%	7,00%	9,00%

10 Valuation

We have chosen several methods to promote ABL Diagnostics, because while the company is active in the field of diagnostics, it develops and markets several types of products, including the preparation of libraries for the SNG, as well as software for the analysis of the results of the SNG, or the management of patient data. Thus, it is in this multiplicity of diagnostic tests, interpretation capacity (software) and development of new proprietary products that a large part of ABL Diagnostics' value lies.

10.1 Determining the discount rate

The discount rate corresponds to the average cost between the cost of equity and the cost of financial debt, weighted according to the importance of these two resources in the overall financing of the company. The cost of equity was determined on the basis of the CAPM model with a Small Cap risk premium embedded in the following formula:

Cost of Equity = Rf +beta * (Rm-Rf) + Prime Small Caps

with Rf : risk-free rate (Rm-Rf) : equity market premium

Indeed, given the size of the company, we assign a Small Caps risk premium to the cost of equity. The Small Caps premium is determined according to 6 criteria, the evaluation of which is factual and objective. The rating scale for each criterion has 5 levels ranging from - - to ++. Each crossing of the threshold adds 20 basis points to the cost of equity.
The criteria are assessed as follows:

Criterion	Rating scale				
	++	+	=	-	--
Corporate Governance[60]	4	3	2	1	0
Liquidity[61]	[66 % ; 100 %]	[33 % ; 66 %[	[15 % ; 33 % [	[5 % ; 15 % [	[0 % ; 5 % [
Gross Margin Size (€ M)	[150 ; +∞ [	[100 ; 150[	[50 ; 100[	[25 ; 50[	[0 ; 25[
Operating profitability	[25 % ; 100 %]	[15 % ; 25 % [	[8 % ; 15 % [	[3 % ; 8 % [	[0 % ; 3 % [
Gearing	] -∞ % ; -15 %]	] -15 % ; 15 %]	]15 % ; 50 %]	]50 % ; 80 %]	]80 % ; +∞ [
Customer Risk[62]	[0 % ; 10 %]	]10 % ; 20 %]	]20 % ; 30 %]	]30 % ; 40 %]	]40 % ; 100 %]

In the case of ABL Diagnostics, we obtain the following matrix:

	++	+	=	-	--	Small Caps Premium
Corporate Governance						0,80%
Liquidity						0,60%
Size of turnover						1,00%
Operating Profitability						0,20%
Gearing						0,80%
Customer Risk						1,00%
TOTAL						**4,40%**

Therefore, based on a risk-free rate of 2.88% (OAT TEC 10 – source: FactSet, Agence France Trésor), a risk premium of 4.2% (premium calculated by Market Risk Premia), a beta of 1.05, a Small Caps risk premium of 5,0% and with a financial leverage of 4.4%, the company's debt as of January 3, 2024, The discount rate is 12%.

Risk free rate	Risk premium	Beta	Small Caps Risk Premium	Cost of Capital	Cost of Debt	Financial leverage	Tax rate	WACC
2,88%	4,2%	1,05	5,0%	12,3%	4,9%	4,4%	25,0%	12,0%

Source : FactSet, Agence France Trésor, Fairness Finance, Market Risk Premia, Damodaran, estimations IEF

[60] The quality of corporate governance is assessed according to the following four criteria: separation of the functions of Chairman and Chief Executive Officer or operation on the basis of a Supervisory Board and a Management Board; presence of independent members on the Board of Directors or the Supervisory Board; presence of censors or control bodies; existence of specialized committees.
[61] The rate of capital turnover over the course of a year.
[62] Share of gross margin accounted for by the 5 largest customers.

10.2 rNPV of the different activities

10.2.1 rNPV des test VIH

Our sales scenario for HIV tests is relatively conservative by preferentially marketing laboratories working on drug resistance. The company's first focus is on the European continent, then from 2026 after approval by the FDA, ABL Diagnostics will start marketing in the USA according to its model, for direct and indirect sales. We believe that the sales growth rate in Europe should be continuously around 40%/year over a period of about five years, while in the USA, the trend should be faster in the first few years in the order of 50%. The price of the test is €618, as it uses several technologies (PCR, Sanger and SNG). The probability of success that we apply is 80%.

MDR-HIV	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
EU-25	3,2	4,0	5,2	7,3	10,2	13,8	18,4	24,0	30,8	38,5
Amerique du Nord	0,0	0,0	0,9	1,1	1,5	2,1	3,0	4,2	6,1	9,2
Ventes totales	**3,2**	**4,0**	**6,1**	**8,4**	**11,7**	**15,9**	**21,4**	**28,2**	**36,9**	**47,7**
Couts des ventes	0,6	0,8	1,2	1,7	2,3	3,2	4,3	5,6	7,4	9,5
Marge Brute	**2,5**	**3,2**	**4,8**	**6,7**	**9,4**	**12,8**	**17,1**	**22,5**	**29,5**	**38,2**
Dépenses opérationnelles	0,4	0,5	0,7	1,0	1,4	2,0	2,6	3,5	4,5	5,8
EBIT	2,2	2,7	4,1	5,7	7,9	10,8	14,5	19,1	25,0	32,3
EBIT margin(%)	*67,75%*	*67,75%*	*67,75%*	*67,75%*	*67,75%*	*67,75%*	*67,75%*	*67,75%*	*67,75%*	*67,75%*
CIR /Impôts	0,0	0,0	0,0	0,0	1,6	2,2	2,9	3,8	5,0	6,5
Capex	0,0	0,1	0,1	0,1	0,2	0,2	0,3	0,4	0,5	0,6
Depreciations/Amortissements	-0,1	0,1	0,1	0,1	0,2	0,3	0,4	0,5	0,6	0,8
Variation BFR	-0,5	-0,7	-0,4	0,0	-0,2	-0,2	-0,2	-0,1	-0,1	-0,1
Free Cash Flow opérationnels	1,5	2,1	3,9	6,0	6,5	8,9	12,0	16,0	21,0	27,2
WACC	12,0%									
FCF opérationnels actualisés	1,2	1,5	2,5	3,4	3,3	4,0	4,9	5,8	6,8	7,9
Valeur terminale	165,7									
Valeur terminale actualisée	19,8									
VAN	**61,1**									
PdS	80,00%									
NPV ajusté au risque	**48,9**									
Nb d'actions	16,11									
rNPV/Action	3,03									

Source : Estimations IE Finance

In this conservative or baseline scenario, the NPV adjusted for the marketing risk of drug resistance tests reaches €**48.9** million, or **€3.03/share**.

10.2.2 rNPV des tests TB

We considered that the diagnostic kits for antibiotic resistance of mycobacterium, an agent of tuberculosis, could be one of the factors in the growth of ABL Diagnostics' activity, especially after the numerous warnings from the WHO with regard to this pathology. Our sales scenario for TB resistance tests is also relatively conservative since we estimate that the marketing of these tests will only take place in Europe initially (CE marking obliges) to healthcare players in Europe, preferably targeting laboratories working on drug resistance.

MDR-TB	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
EU	0,7	0,8	1,1	1,4	1,9	2,6	3,6	5,3	7,9	11,9
USA	0,0	0,0	0,4	0,5	0,7	1,1	1,6	1,9	1,9	1,9
Ventes totales	**0,7**	**0,8**	**1,5**	**1,9**	**2,6**	**3,6**	**5,2**	**7,2**	**9,8**	**13,8**
Couts des ventes	0,1	0,2	0,2	0,3	0,3	0,4	0,4	0,4	0,4	0,6
Marge Brute	**0,6**	**0,7**	**1,2**	**1,6**	**2,3**	**3,3**	**4,8**	**6,7**	**9,4**	**13,3**
Dépenses opérationnelles	0,1	0,1	0,2	0,2	0,3	0,4	0,6	0,9	1,2	1,7
EBIT	0,5	0,6	1,1	1,4	1,9	2,8	4,1	5,9	8,2	11,6
CIR /Impôts	-0,9	-0,9	-0,8	0,0	0,4	0,6	0,8	1,2	1,6	2,3
Capex	0,0	0,0	0,0	0,0	0,0	0,1	0,1	0,1	0,2	0,2
Depreciations/Amortissements	-0,1	0,0	0,0	0,0	0,0	0,1	0,1	0,1	0,2	0,2
Variation BFR	-0,5	-0,7	-0,4	0,0	-0,2	-0,2	-0,2	-0,1	-0,1	-0,1
Free Cash Flow opérationnels	0,8	0,8	1,5	1,5	1,4	2,1	3,3	4,8	6,8	9,6
WACC	12,0%									
FCF opérationnels actualisés	0,6	0,6	1,0	0,9	0,7	1,0	1,3	1,7	2,2	2,8
Valeur terminale	59,8									
Valeur terminale actualisée	7,1									
VAN	**19,9**									
PdS	80,00%									
NPV ajusté au risque	**15,9**									
Nb d'actions	16,11									
rNPV/Action	0,99									

Source : Estimations IE Finance

From 2026 after approval by the FDA, ABL Diagnostics will begin marketing in the USA according to its model, for direct and indirect sales. We believe that the rate of sales growth in Europe will be very rapid, particularly because of the mechanisms of co-infection with HIV (>100% over the first five years). The same will be true from 2026 in the USA. The price of the test is €80, with an 80% probability of success. In this prudent or baseline scenario, the

NPV adjusted for the marketing risk of mycobacterium drug resistance tests reached €**15.9** million, or **€.99/share**.

10.2.3 rNPV of the activity "Preparing libraries" (basic scenario)

Declining sequencing costs, increasing incidence of genetic and infectious diseases, increasing use of NGS in diagnostics, and increasing R&D and healthcare spending are all factors that we believe are driving the NGS library preparation market. In addition, there is an increase in the number of applications and companies working in the SNG. This is why we have chosen to independently value this activity as one of the growth factors for ABL Diagnostics.

Bibliothèque	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
EU-26	0,0	0,0	0,1	0,2	0,3	0,4	0,6	0,9	1,4	2,0
USA + Canada	0,0	0,0	0,0	0,3	0,5	0,9	1,5	2,2	3,3	4,8
Asie-Pacifique	0,0	0,0	0,0	0,4	0,7	1,2	2,1	3,1	3,0	4,4
Ventes totales	**0,0**	**0,0**	**0,1**	**0,7**	**1,2**	**2,1**	**3,6**	**5,3**	**6,3**	**9,3**
Couts des ventes	0,0	0,0	0,0	0,1	0,1	0,2	0,3	0,3	0,3	0,4
Marge Brute	**0,0**	**0,0**	**0,1**	**0,6**	**1,1**	**1,9**	**3,3**	**5,0**	**6,0**	**8,9**
Dépenses opérationnelles	0,0	0,0	0,0	0,1	0,1	0,3	0,4	0,6	0,8	1,1
EBIT	0,0	0,0	0,1	0,5	0,9	1,7	2,9	4,3	5,3	7,8
CIR /Impôts	-0,9	-0,9	-0,8	0,0	0,2	0,3	0,6	0,9	1,1	1,6
Capex	0,0	0,0	0,0	0,0	0,0	0,0	0,1	0,1	0,1	0,1
Depreciations/Amortissements	-0,1	0,0	0,0	0,0	0,0	0,0	0,1	0,1	0,1	0,2
Variation BFR	-0,5	-0,7	-0,4	0,0	-0,2	-0,2	-0,2	-0,1	-0,1	-0,1
Free Cash Flow opérationnels	0,3	0,2	0,5	0,6	0,6	1,2	2,2	3,5	4,3	6,4
WACC	11,4%									
FCF opérationnels actualisés	0,2	0,2	0,3	0,3	0,3	0,5	0,9	1,3	1,5	2,0
Valeur terminale	40,1									
Valeur terminale actualisée	4,6									
VAN	**12,2**									
PdS	80,00%									
NPV ajusté au risque	**9,7**									
Nb d'actions	16,11									
rNPV/Action	0,60									

Source : Estimations IE Finance

This growth is expected to take place mainly in the US and China. First of all because the USA represents a majority share in the use of the SNG and then because China with the MGI partnership could be one of the natural development markets for this library production activity for the SNG. In this baseline scenario, the risk adjusted NPV for the marketing of SNG's libraries is €**9.7** million, or **€0.60/share**.

10.2.4 rNPV of oncology business

Lower sequencing costs are a positive for greater adoption of NGS techniques in oncology, but ABL diagnostics will face greater competition than in other segments where it operates. However, ABL Diagnostics is expected to capitalize on its experience and expertise in infectious diseases as well as its data integration software

Oncology	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
EU-25	0,2	0,3	0,9	1,4	2,2	3,5	5,5	8,6	11,3	14,8
USA	0,0	0,1	0,1	0,1	0,2	0,4	0,6	0,8	1,3	1,89
Ventes totales	**0,2**	**0,4**	**0,9**	**1,5**	**2,4**	**3,8**	**6,0**	**9,5**	**12,6**	**16,7**
Couts des ventes	0,0	0,1	0,1	0,2	0,3	0,4	0,5	0,6	0,5	0,7
Marge Brute	**0,2**	**0,4**	**0,8**	**1,3**	**2,1**	**3,4**	**5,5**	**8,9**	**12,0**	**16,0**
Dépenses opérationnelles	0,02	0,05	0,11	0,18	0,28	0,46	0,72	1,13	1,51	2,00
EBIT	0,1	0,3	0,7	1,1	1,8	3,0	4,8	7,8	10,5	14,0
CIR /Impôts	-0,9	-0,9	-0,8	0,0	0,4	0,6	1,0	1,6	2,1	2,8
Capex	0,0	0,0	0,0	0,0	0,0	0,1	0,1	0,1	0,2	0,3
Depreciations/Amortissements	-0,1	0,0	0,0	0,0	0,0	0,1	0,1	0,2	0,2	0,3
Variation BFR	-0,5	-0,7	-0,4	0,0	-0,2	-0,2	-0,2	-0,1	-0,1	-0,1
Free Cash Flow opérationnels	0,4	0,5	1,1	1,2	1,3	2,3	3,8	6,4	8,7	11,6
WACC	12,0%									
FCF opérationnels actualisés	0,3	0,4	0,7	0,7	0,6	1,0	1,6	2,3	2,8	3,4
Valeur terminale	61,4									
Valeur terminale actualisée	7,3									
VAN	**21,1**									
PdS	80,00%									
NPV ajusté au risque	**16,9**									
Nb d'actions	16,11									
rNPV/Action	1,05									

This growth is expected to take place mainly in the US and China. First of all because the USA represents a majority share in the use of the SNG and then because China with the MGI partnership could be one of the natural development markets for this library production activity for the SNG. In this baseline scenario, the risk adjusted NPV for the marketing of SNG's libraries is €**16.9** million, or **€1.05/share**.

10.2.5 rNPV of the NADIS® (Digital Health) activity

The NADIS® electronic medical record, developed by ABL Diagnostics, also seems to us to be a possible growth lever. This tool, which allows the daily monitoring of HIV-positive patients, includes several sections intended for the entire medical community, including caregivers, while offering the possibility of making prescriptions. This

computerized medical record is used in more than 200 French and African hospitals, mainly in French-speaking Africa. Although this activity currently represents only 9% of ABL Diagnostics' overall turnover, we believe that it is set to grow.

Nadis	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
France	0,6	0,6	0,6	0,6	0,6	0,7	0,7	0,7	0,7	0,7
EU-26	0,0	0,0	0,0	0,1	0,2	0,4	0,7	0,9	1,2	1,4
Ventes totales	**0,6**	**0,6**	**0,7**	**0,7**	**0,8**	**1,0**	**1,4**	**1,6**	**1,9**	**2,2**
Couts des ventes	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1
Marge Brute	**0,5**	**0,5**	**0,6**	**0,6**	**0,7**	**0,9**	**1,3**	**1,5**	**1,8**	**2,1**
Dépenses opérationnelles	0,1	0,1	0,1	0,1	0,1	0,1	0,2	0,2	0,2	0,3
EBIT	0,4	0,4	0,5	0,5	0,6	0,8	1,1	1,3	1,6	1,8
CIR /Impôts	-0,9	-0,9	-0,8	0,0	0,1	0,2	0,2	0,3	0,3	0,4
Capex	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
Depreciations/Amortissements	-0,1	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
Variation BFR	-0,5	-0,7	-0,4	0,0	-0,2	-0,2	-0,2	-0,1	-0,1	-0,1
Free Cash Flow opérationnels	0,7	0,7	0,9	0,6	0,3	0,5	0,7	1,0	1,2	1,4
WACC	11,4%									
FCF opérationnels actualisés	0,6	0,5	0,6	0,3	0,2	0,2	0,3	0,4	0,4	0,4
Valeur terminale	8,8									
Valeur terminale actualisée	1,0									
VAN	**4,9**									
PdS	80,00%									
NPV ajusté au risque	**3,9**									
Nb d'actions	16,11									
rNPV/Action	0,24									

Source : Estimations IE Finance

In our base case, the risk adjusted NPV for the marketing of NADIS® software to hospitals and other care facilities is **€3.9** million, representing a contribution of **€0.24/share**.

10.3 Company DCF

In order to take into account the fact that ABL Diagnostics markets its tests as well as its software, thus generating revenues, we use the method of discounting cash flows by discounting Free Cash-Flow to Equity (DCF). With an initial period of 10 years in 2024E and 2033E which should correspond to the marketing of ABL's various tests on its international markets and the beginning of the attack on the US market.
The main assumptions of this scenario are as follows:

- **Sales:** sales of ABL Diagnostics' tests are growing very quickly. The growth rate is very fast cumulatively of 123% between 2024E and 2027E and then maintains a practically constant pace at 36% growth after 2028.
- **Operating profitability:** Although ABL Diagnostics' objective is to reach operational breakeven quickly, the operating margin is only expected to become positive in 2029E and should then average 21% over the period 2029E – 2033E. Indeed, the strong growth in sales will make it possible to compensate for the significant expenses (marketing, SG&A). We should see a steady improvement in operating margin over the years.
- **Corporate tax:** the tax rate is 25%
- **Working capital requirements:** 15% of sales
- **Discount rate:** We therefore apply a discount rate of 12% in our model (see above).
- **Infinite Growth Rate:** 1%

With a discount rate of 12 %, we obtain the following free cash flow statement (in € million):

	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E
Chiffre d'Affaires	6,3	8,5	12,7	17,7	24,4	33,2	45,5	61,1	78,1	101,6
REX (EBIT)	1,0	2,0	2,6	4,3	5,7	7,4	9,8	13,0	16,1	20,2
Impots	-0,3	-0,3	-0,3	-0,3	-0,3	-0,3	3,3	-4,2	-5,1	-6,2
Amortissements Provisions	0,7	1,5	2,4	2,6	2,9	3,2	3,5	3,9	4,2	4,7
Investissements	-0,4	-0,4	-0,4	-0,4	-0,4	-0,4	-0,4	-0,4	-0,4	-0,4
Variation BFR	2,7	0,3	0,4	0,4	-5,0	0,0	0,1	0,0	0,0	0,0
FCF opérationnels	-1,7	0,9	4,7	6,7	2,8	9,9	16,4	12,3	14,8	18,3
FCF opérationnels actualisés	-1,4	0,8	3,9	5,6	2,4	8,3	13,7	10,3	12,4	15,3

Source : Estimations IE Finance

Over the post-forecast period, we apply an infinite growth rate, in two stages, and obtain the following forecasts (in € million):

FCF actualisés 2024-2033	71,1
+ Valeur Terminale actualisée	118,6
+ Titres Financiers	0,1
+ Titres mis en équivalence	0,0
- Provisions	0,0
- Endettement financier net	-0,6
- Minoritaires	0,0
+ Reports déficitaires actualisés	-0,3
= Valeur des Capitaux Propres pg (VE)	**188,8**
Nombre d'actions	16,1
Valeur par action (EUR)	**11,7**

Thus, the discounted cash flow method shows an indicative value of equity for ABL Diagnostics of **€188.82 million,** or **€11.72 per** share.

10.4 Comparable

We chose a sample of companies active in the field of in vitro diagnostics and molecular diagnostics. However, within the sample, there is a great disparity in terms of turnover, capitalization and financial ratios.

10.4.1 Comparable valuation (Small Cap)

Our first sample is made up of companies like Biosynex, Eurobio Scientific, Eurofins, Ikonisys, Novacyt, Genetic Signatures, Genetic Technologies, MDx Health, Myriad, Natera, OpGen, OPKO Health, Sophia Genetics, Veracyte.

The table below summarizes the main aggregates, in € million, of the companies in our sample:

In EUR	CA	CA	CA	CA	EBE	EBE	EBE	EBE	REX	REX	REX	REX	RN	RN	RN	RN
	FY0	FY1	FY2	FY3	FY0	FY1	FY2	FY3	FY0	FY1	FY2	FY3	FY0	FY1	FY2	FY3
Biosynex	3 674,7	3 898,6	4 185,9	4 498,2	795,1	NS	NS	NS	535,7	614,9	695,0	774,3	322,8	465,8	524,6	594,6
Eurobio Scientific	130,0	138,0	148,1	156,2	23,3	NS	NS	NS	10,1	25,3	28,8	32,2	4,8	9,8	11,0	13,7
Eurofins	6 514,6	7 049,2	7 569,5	8 101,4	1 211,1	NS	NS	NS	546,8	902,4	1 039,1	1 150,1	423,3	520,1	622,9	724,9
Ikonisys	3,6	NS	NS	NS	-0,4	NS	NS	NS	-0,8	NS	NS	NS	-2,9	NS	NS	NS
Novacyt	13,3	NS	NS	NS	-15,8	NS	NS	NS	-20,6	NS	NS	NS	-32,0	NS	NS	NS
Genetic Signatures	16,9	NS	NS	NS	-17,4	NS	NS	NS	-18,9	NS	NS	NS	-14,1	NS	NS	NS
Genetic Technologuies	8,7	NS	NS	NS	-11,1	NS	NS	NS	-11,8	NS	NS	NS	-11,9	NS	NS	NS
MDx Health	70,2	84,0	95,6	NS	-20,0	NS	NS	NS	-26,9	-19,6	-9,3	-0,4	-27,3	-27,9	-19,1	-10,7
Myriad	753,2	832,0	892,8	950,7	-71,4	23,1	52,0	81,7	-144,6	3,4	24,3	53,6	-263,3	3,2	20,6	40,0
Natera	1 082,6	1 433,8	1 678,1	1 961,2	-405,0	-281,2	-119,9	47,5	-443,6	-312,6	-157,9	-21,8	-434,8	-297,3	-144,7	-6,5
OpGen	3,4	NS	NS	NS	-14,4	NS	NS	NS	-15,7	NS	NS	NS	-65,3	NS	NS	NS
OPKO Health	863,5	715,1	754,0	854,5	-52,8	NS	NS	NS	-158,1	-239,3	-174,9	-34,5	-188,9	-264,7	-195,2	-40,7
Sophia Genetics	62,4	79,1	102,0	132,1	-68,6	NS	NS	NS	-76,9	-61,7	-49,6	-37,7	-78,5	-57,8	-50,5	-39,1
Veracyte	361,1	NS	NS	NS	15,1	NS	NS	NS	-12,1	NS	NS	NS	-74,4	NS	NS	NS

Source: IE Finance based on FactSet as of 6/24

In EUR	Market cap.	Net debt 23	Minorities 21	EV
Biosynex	35,9	166,4	-34,8	167,5
Eurobio Scientific	144,1	11,6	0,0	155,7
Eurofins	10 177,8	3 705,5	-2,5	13 880,8
Ikonisys	9,1	7,6	0,0	16,7
Novacyt	41,1	-35,0	0,0	6,1
Genetic Signatures	98,5	-16,3	0,0	82,1
Genetic Technologuies	7,6	-7,3	0,0	0,2
MDx Health	67,2	18,9	0,0	86,1
Myriad	2 055,5	10,0	0,0	2 065,5
Natera	12 313,6	-437,0	0,0	11 876,6
OpGen	3,0	11,9	0,0	14,9
OPKO Health	796,0	230,7	0,0	1 026,7
Sophia Genetics	288,9	-104,7	0,0	184,2
Veracyte	1 613,1	-203,8	0,0	1 409,3

Source: IE Finance based on FactSet as of 3/24

The table below details the main stock market multiples of the comparable companies in our sample, restated via the acronym "NS" for unavailable stocks.

	VE/CA	VE/CA 25E	VE/CA 26E	VE/ EBE 24E	VE/ EBE 25E	VE/ EBE 26E	VE/REX 24E	VE/REX 25E	VE/REX 26E	PE 22	PE 23
	FY1	FY2	FY3	FY1	FY2	FY3	FY1	FY2	FY3		
Biosynex	0,0	0,0	0,0	NS	NS	NS	0,3	0,2	0,2	0,1	0,1
Eurobio Scientific	1,1	1,1	1,0	NS	NS	NS	6,2	5,4	4,8	14,7	13,1
Eurofins	2,0	1,8	1,7	NS	NS	NS	15,4	13,4	12,1	19,6	16,3
Ikonisys	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Novacyt	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Genetic Signatures	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Genetic Technologuies	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
MDx Health	1,0	0,9	NS	NS	NS	NS	-4,4	-9,2	-222,0	-2,4	-3,5
Myriad	2,5	2,3	2,2	89,5	39,7	ns	600,4	85,1	38,5	637,3	99,9
Natera	8,3	7,1	6,1	-42,2	-99,1	249,8	-38,0	-75,2	-546,0	-41,4	-85,1
OpGen	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
OPKO Health	1,4	1,4	1,2	NS	NS	NS	-4,3	-5,9	-29,8	-3,0	-4,1
Sophia Genetics	2,3	NS	NS	NS	NS	NS	-3,0	-3,7	-4,9	-5,0	-5,7
Veracyte	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

Source: IE Finance based on FactSet as of 1/2/24

The table below shows the induced valuations (in € million) according to the multiples applied on the basis of the current valuations displayed by the companies in the sample.

	Sales FY1E	Sales FY2E	Sales FY3E	EBE FY1E	EBE FY2E	EBE FY3E	REX FY1E	REX FY2E	REX FY3E	RN FY1E	RN FY2E
ABL Diagnostics	6,3	8,5	12,7	1,0	2,0	2,6	-0,3	3,5	5,0	0,0	3,8
Average Valuation/ share		**1,03**			12,51			-0,50		0,12	
Average	**3,29**										

Thus, the approach based on the method of comparable Small Cap stock market multiples leads us to a valuation **of €3.29/share,** i.e. a capitalization of **€53.01 million.**

10.4.2 Comparable valuations (large cap)

Our second sample is made up of larger companies active in IVD and molecular diagnostics as well as genotyping assays, NGS and sequencers such as Agilent, Becton, BioRad, Hologic, Illumina, Oxford Nanopore, Qiagen Stryker, ThermoFisher.

The table below summarizes the main aggregates, in € million, of the companies in our sample:

In EUR	CA	CA	CA	CA	EBE	EBE	EBE	EBE	REX	REX	REX	REX	RN	RN	RN	RN
	FY0	FY1	FY2	FY3	FY0	FY1	FY2	FY3	FY0	FY1	FY2	FY3	FY0	FY1	FY2	FY3
Agilent	6 833,0	6 458,7	6 832,4	7 305,1	1 899,0	1 888,2	2 060,4	2 231,1	1 628,0	1 721,4	1 897,6	2 061,6	1 240,0	1 524,5	1 658,5	1 792,2
Becton	19 372,0	20 231,9	21 403,7	22 618,2	4 357,0	5 736,3	6 628,9	7 137,1	2 196,0	4 883,2	5 319,0	5 765,1	1 530,0	3 795,0	4 156,9	4 572,3
BioRad	2 671,3	2 652,8	2 791,5	2 899,2	576,2	471,1	526,0	566,1	383,8	345,4	395,5	435,4	-637,3	294,7	329,9	366,2
Hologic	4 030,4	4 032,8	4 252,6	4 499,1	1 264,4	1 331,8	1 434,2	1 528,6	941,0	1 230,9	1 331,2	1 426,0	456,0	968,0	1 045,1	1 131,2
Illumina	4 504,0	4 489,3	4 815,2	5 193,4	338,0	484,2	672,4	1 026,7	-94,0	240,4	432,5	707,7	-1 161,0	144,6	297,5	448,4
Oxford Nanopore	169,7	185,4	237,7	300,7	-128,4	-94,6	-72,1	-40,6	-170,0	-152,2	-131,1	-100,9	-149,8	-148,8	-128,8	-95,5
Pacific Bioscience	200,5	180,9	235,8	319,1	-277,7	-233,2	-174,0	-110,0	-310,4	-250,1	-199,5	-151,3	-306,7	-254,2	-204,1	-156,4
Qiagen	1 965,3	2 001,7	2 127,7	2 278,3	650,6	704,2	775,2	844,5	445,2	560,4	612,5	670,6	341,3	476,2	513,3	563,7
Stryker	20 498,0	22 307,2	24 050,2	25 885,2	5 309,0	6 087,8	6 759,7	7 416,5	4 281,0	5 614,8	6 287,2	6 882,3	3 165,0	4 602,0	5 167,0	5 692,6
Thermo Fisher	42 857,0	42 973,3	46 113,4	49 478,0	10 852,0	10 814,1	11 874,9	13 056,5	7 446,0	9 723,0	10 740,7	11 771,5	5 955,0	8 318,5	9 230,9	10 145,4

Source: IE Finance based on FactSet as of 3/24

In EUR	Market cap.	Net debt 23	Minorities 21	EV
Agilent	36 395,0	1 309,0	0,0	37 704,0
Becton	64 470,5	14 921,0	0,0	79 391,5
BioRad	7 698,0	-207,0	0,0	7 491,1
Hologic	15 964,1	181,6	0,0	16 145,7
Illumina	16 191,0	1 208,0	0,0	17 399,0
Oxford Nanopore	953,5	-228,4	0,0	725,1
Pacific Bioscience	374,8	302,2	0,0	677,0
Qiagen	8 693,6	553,3	0,0	9 247,0
Stryker	122 194,9	10 441,0	0,0	132 635,9
Thermo Fisher	201 757,2	28 341,0	-40,0	230 058,2

Source: IE Finance based on FactSet as of 3/24

The table below details the main stock market multiples of the comparable companies in our sample, restated via the acronym "NS" for unavailable stocks.

	VE/CA	VE/CA	VE/CA	VE/ EBE	VE/ EBE	VE/ EBE	VE/REX	VE/REX	VE/REX	PE	PE
	FY1	FY2	FY3	FY1	FY2	FY3	FY1	FY2	FY3	FY1	FY2
Agilent	5,8	5,5	5,2	20,0	18,3	16,9	21,9	19,9	18,3	23,9	21,9
Becton	3,9	3,7	3,5	13,8	12,0	11,1	16,3	14,9	13,8	17,0	15,5
BioRad	2,8	2,7	2,6	15,9	14,2	13,2	21,7	18,9	17,2	26,1	23,3
Hologic	4,0	3,8	3,6	12,1	11,3	10,6	13,1	12,1	11,3	16,5	15,3
Illumina	3,9	3,6	3,4	35,9	25,9	16,9	72,4	40,2	24,6	111,9	54,4
Oxford Nanopore	3,9	3,1	2,4	-7,7	-10,1	-17,9	-4,8	-5,5	-7,2	-6,4	-7,4
Pacific Bioscience	3,7	2,9	2,1	-2,9	-3,9	-6,2	-2,7	-3,4	-4,5	-1,5	-1,8
Qiagen	4,6	4,3	4,1	13,1	11,9	11,0	16,5	15,1	13,8	18,3	16,9
Stryker	5,9	5,5	5,1	21,8	19,6	17,9	23,6	21,1	19,3	26,6	23,6
Thermo Fisher	5,4	5,0	4,6	21,3	19,4	17,6	23,7	21,4	19,5	24,3	21,9

Source: IE Finance based on FactSet as of 3/24

The table below shows the induced valuations (in € million) according to the multiples applied on the basis of the current valuations displayed by the companies in the Large Cap sample.

	Sales FY1E	Sales FY2E	Sales FY3E	EBE FY1E	EBE FY2E	EBE FY3E	REX FY1E	REX FY2E	REX FY3E	RN FY1E	RN FY2E
ABL Diagnostics	6,3	8,5	12,7	1,0	2,0	2,6	-0,3	3,5	5,0	0,0	3,8
Average valuation/share		**2,24**			**1,39**			**2,52**		2,23	
Average	**2,09**										

Source: IE Finance based on FactSet as of 3/24

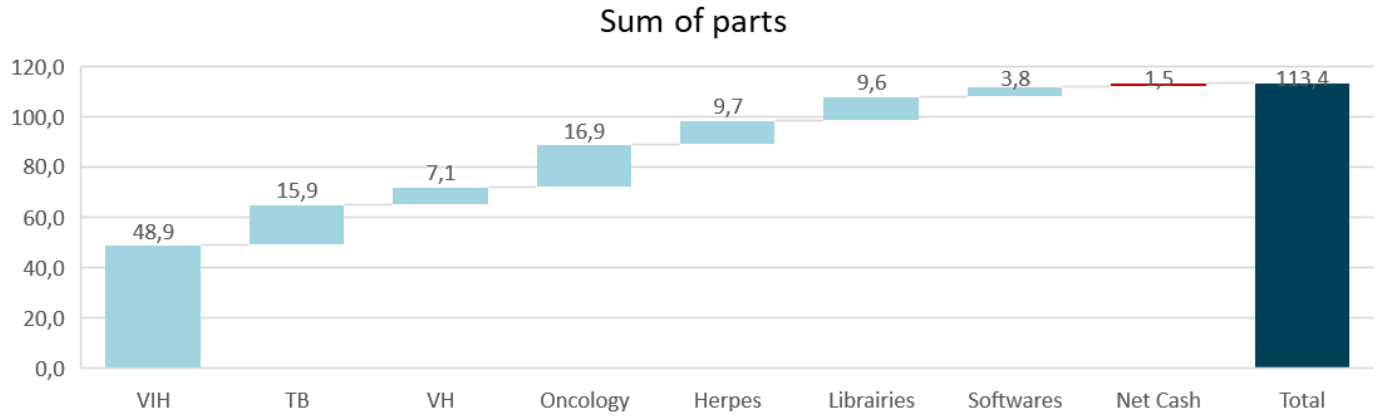
Thus, the approach using the Large Cap comparable stock market multiples method leads us to a valuation of **€2.09/share,** i.e. a capitalization of **€33.74 million.**

10.5 Synthesis

The value of the company is determined according to the different methods used (risk adjusted NPV, overall portfolio DCF and comparable methods: SC and LC).

Methods	Value	Value/share
Comp LC	33,74	2,09
Comp SC	53,01	3,29
rNPV	111,88	6,94
DCF	188,82	11,72
Moyenne (M€)	96,86	6,01

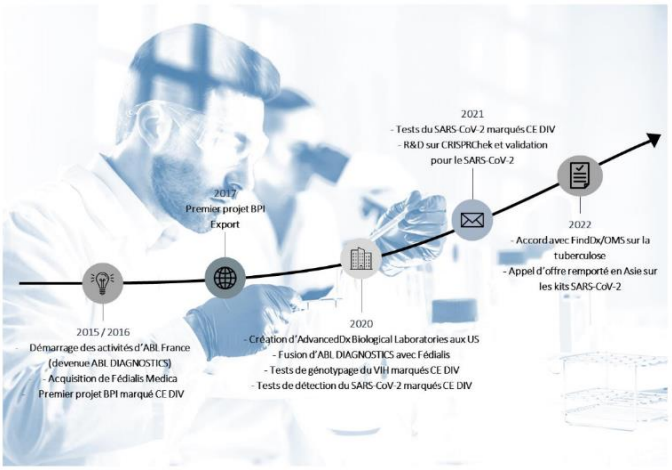
In total, the value for the base scenario stands at €6.01 per share, which reflects an upside potential of around 114.7 % compared to the current level (€2.80).



Most of the valuation is to be credited to the HIV business, which is expected to contribute 43.7%, followed by two activities: the determination of *mycobacterial* (TB) resistance and oncology, which should eventually represent 14.2% and 15.2% respectively, reflecting the growing interest of health authorities, in particular the WHO, in these two indications.

11 Annexes

11.1 History of ABL Diagnostics



In 2015, ABL SA created ABL France ("Advanced Biological Laboratories Fedialis") by way of a contribution in kind by ABL SA of its activity of developing diagnostic test kits by genotyping for infectious diseases. ABL France is now a company specializing in molecular detection and genotyping diagnostics for infectious diseases.

In 2016, ABL SA acquired Fedialis Medica (France) from the GlaxoSmithKline (GSK) group. Fedialis Medica has developed a shared electronic medical record system for the management of patients with infectious diseases (Nadis™ Solution). Fedialis Medica was merged in the 2020 financial year into ABL France.

In 2019, ABL SA created ABL AdvancedDX Biological Laboratories USA Inc. (a 100% subsidiary of ABL France) in charge of marketing, since 2020, its test kits throughout North America. ABL has entrusted ABL France, its 100% subsidiary, with the mission of designing, developing, manufacturing and marketing in vitro diagnostic medical devices for some of its RUO products, in particular for HIV-1 since the software components exist.

In 2020, ABL Diagnostics merged with Fedialis Medica. CE markings of the HIV genotyping test and the detection of SARS-Cov2.

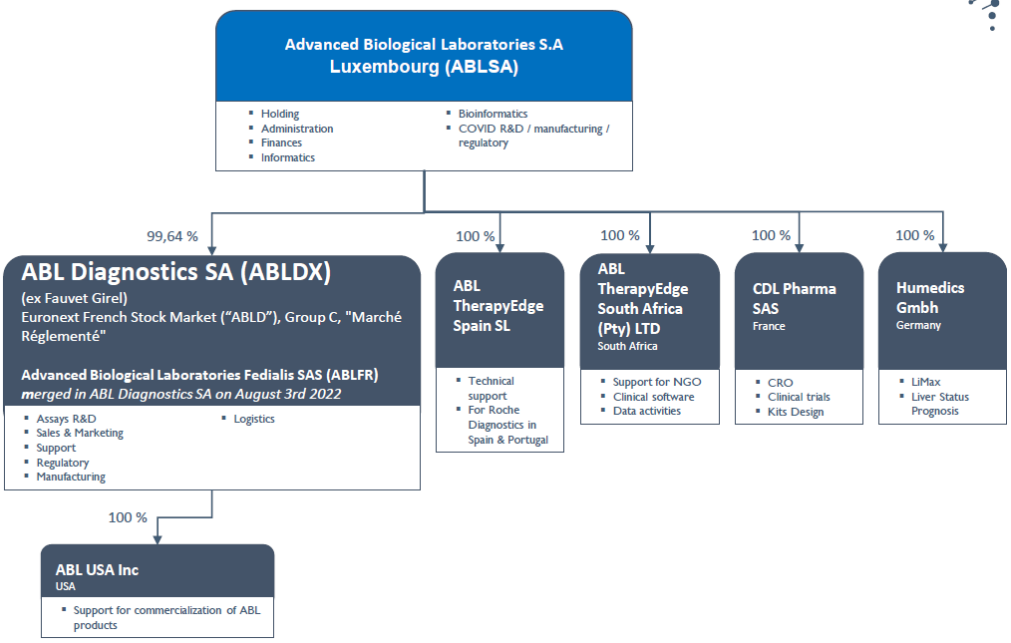
In 2021, commercialization of the SARS-Cov-2 IVD test and development and validation of the CRISPRChek® test for SARS-Cov2.

In 2022, ABL France became ABL Diagnostics and listed on the Midcap market of Euronext Paris. Continued commercialization of the SARS-Cov-2 IVD test. Commercialization of two new CE-marked assays: for Whole Genome sequencing for HIV, as well as for mycobacterium genotyping in tuberculosis. October 2022: ISO 13485 certification of ABL Diagnostics' Marseille site.

In December 2022, ABL acquired a medical device company in Germany, Humedics GmbH, which is dedicated to managing liver transplant patients who require liver function assessments.

11.2 Organization

ABL Diagnostics, a subsidiary and only listed company of the Luxembourg Advanced Biological Laboratories SA group, which includes subsidiaries in Spain, South Africa and Germany. ABL Diagnostics also has a subsidiary in the United States, ABL USA Inc., which is involved in the marketing of ABL Diagnostics' products in the Americas.



11.3 Governance: Management and Committee

The company is made up of about twenty people, including a sales force of about ten employees, who participate in the marketing of the entire range of ABL Diagnostics products. The management is mainly composed of three managers:

Dr. Chalom Sayada, founder and CEO: doctor trained in part at the Robert Debré Hospital, formerly of Roche, founder of ACT Gene in the AIDS genotype, sold to the Canadian group Visible Genetics of which he took over the management for Europe for two years. In 2000, he co-founded ABL in Luxembourg, to develop TherapyEdge, a software combining computer science and biotechnology. Then came the creation of Integrated Therapeutic Systems (ITS) to manage the data accumulated by virologists and clinicians.

Ronan Boulmé, Director of Compliance (Quality and Regulatory): holder of an Inter-University Diploma in Clinical Research Statistics, a DUT in Data Management & Statistics, and more recently a DU Data Protection Officer (Paris X), Blockchain certificates (New York University), Ronan BOULME has been Governance, Risk and Compliance (GRC) Director and Quality Management Representative (QMR) since 2019 for the competent authorities in relation to medical devices for the activities of the ABL Group, within ABL FRANCE.

Dimitri Gonzalez, Director of Diagnostic Solutions: With 20 years of experience in the development and marketing of solutions (molecular biology software and products) for microbiology laboratories, Dimitri is the head of the Diagnostics Business Unit of the ABL SA Group, dedicated to clinical diagnostics and personalized medicine. He oversees the R&D teams and their activities (bioinformaticians, laboratory researchers, technicians, quality control managers, web developers), supply chain, marketing and commercialization of a full range of products on a global scale, such as CE-IVD molecular biology tests for HIV genotyping or SARS-CoV-2 detection kits.

Board of Directors

The Chair of the Board is **Noémie SADOUN** : a graduate of the University of Paris Dauphine in 2017, Noémie Sayada Sadoun, a specialist in Agility, is in charge of the roadmap of the access portal and the management of rights to Veolia Environment's applications. Since 2017, she has been working in various product teams in charge of application development for the optimization of activities in France and abroad, as a consultant and then as a full member of Veolia Environment as Product Manager. Previously, she was responsible for testing Accenture's Chorus IS.

Laure RAFFAELLI: She joined ABL S.A. in September 2019 and is Chief Financial Officer. Laure Raffaelli is a chartered accountant with extensive experience in accounting and financial accounting. For more than ten years, she has supported companies with various profiles operating in a variety of sectors.

Deborah SZAFIR: graduated from the Faculty of Medicine of Paris Creteil Val de Marne with 2 years of experience in surgery in French, British and Israeli hospitals as a first intervention assistant, graduated from HEC (2000) and the Advanced Management Program of INSEAD (2016). She is currently Executive Vice President in charge of Medical Affairs and Patient & Consumer Relations at Pierre Fabre. Deborah Szafir brings her knowledge of the pharmaceutical industry to the table with a strong international professional experience in high-level medical positions.

Jean-Christophe RENONDIN : Doctor of Medicine (University of Paris V Descartes, 1989) and holder of an MBA from the Amos Tuck School of Business Administration (Dartmouth College, 1991), Jean-Christophe Renondin is currently Senior Healthcare Manager at the Oman Investment Authority. With extensive experience in venture capital and private equity, particularly in the healthcare sector, he was Managing Director at Bryan, Garnier & Co (2010-2015) and General Partner at Caisse des Dépôts et Consignations Innovation, in the fields of Biopharma, BioTech, diagnostics and MedTech (2005-2010).

Bertrand AULONG : A retired Doctor of Pharmacy, Bertrand Aulong has worked at the Foch Hospital and the Trousseau Hospital. Previously, he was at ABBOTT Diagnostics France, Head of Reagent Registrations at the National Health Laboratory, at ROCHE Diagnostics France, Director of the PCR Molecular Biology Department, Marketing Director (Biochemistry, Immunology, PCR), at Visible Genetics France at BD (Business Development Export) for HIV and HCV sequencing activities for the following areas: Asia, South Africa, At BIOPEP Montpellier, Director of Operations, Production and Distribution of Hemostasis Reagents in France.

Carlos FREIXAS : Biochemist, holder of a master's degree in marketing from the University of Barcelona (Spain), Carlos Freixas Romagosa has a long experience in the medical device and biotechnology industry in Iberia and Latin America in commercial activities, digital marketing and innovation. After starting his career at Boehringer Mannheim, he held various positions at Roche in marketing and research.

12 Summary of accounts

Simplified income statement

31/12 (€m)	2021	2022	2023E	2024E	2025E	2026E
Revenues	**6.27**	**8.75**	**5.61**	**6.3**	**8.52**	**12.74**
Procurements	1.7	1.47	1.31	1.3	1.56	1.71
Staff costs	1.29	1.33	1.46	1.64	2.21	3.31
Other costs	3.01	3.92	4.43	4.68	5.48	8.17
Ebitda	**0.83**	**2.68**	**0.5**	**0.98**	**2.01**	**2.57**
Depreciations & Provisions	0.79	0.56	1.16	1.27	1.52	2.39
Ebit	**0.04**	**2.12**	**-0.66**	**-0.29**	**3.53**	**4.96**
Financial income & charges	0.02	0.02	-0.01	-0.01	-0.02	-0.02
Earnings before tax	**0.07**	**2.13**	**-0.67**	**-0.31**	**3.52**	**4.94**
Income tax	-0.29	-0.29	-0.29	-0.29	-0.29	-0.29
Tax rate (%)	*-1.8%*	*-1.5%*	*-1.5%*	*-1.6%*	*-1.5%*	*-1.5%*
Net earnings	**0.37**	**2.43**	**-0.38**	**-0.01**	**3.81**	**5.23**
Number of shares (in million)	16.11	16.11	46.94	16.11	16.11	16.11
EPS (EUR per share)	**-0.05**	**0.02**	**0.05**	**-0.02**	**0**	**0.24**

Balance sheet – main aggregates

31/12 (M€)	2021	2022	2023E	2024E	2025E	2026E
ASSETS						
Intangible fixed assets	2.13	1.93	2.07	2.45	2.45	2.45
Tangible fixed assets	1.22	1.2	0.96	0.55	0.55	0.55
Long-term investments	0.03	0.29	0.26	0.3	0.3	0.3
Non-current asset	**3.08**	**2.97**	**2.63**	**1.34**	**1.34**	**1.34**
Inventories Merchandise	0.84	0.67	0.71	0	0.1	0.11
Trade receivables	7.21	3.92	3.96	11.36	12.51	13.77
Other receivables	0	5.48	4.1	6.48	6.48	6.48
Cash and cash equivalents	0.6	1.01	2.23	1.55	1.55	1.55
Current assets	**8.67**	**11.08**	**11.01**	**19.39**	**20.64**	**21.9**
TOTAL ASSETS	**12.05**	**14.5**	**14.31**	**22.68**	**23.93**	**25.2**
LIABILITIES						
Share Capital	2.1	1.61	1.61	1.61	1.61	1.61
Additional paid-in capital	0	3.39	3.39	3.39	3.39	3.39
Reserves and consolidated income	1.48	0.22	0.22	0.22	0.22	0.22
Other reserves	1.52	1.11	0.05	-1.53	-1.02	-0.94
Shareholders' equity	**6.08**	**6.75**	**6.77**	**4.15**	**3.07**	**3.66**
Bonds	0.88	0.69	1.87	1.3	1.3	1.3
Bank borrowings	1.98	1.96	1.59	1.72	1.72	1.72
Conditional advances	0	0.01	0	0.01	0.01	0.01
Trade payables	2.27	4.23	3.23	13.56	14.93	16.43
Tax and social security liabilities	0.74	0.5	0.23	1.57	1.73	1.9
Other liabilities	0.07	0.36	0.61	0.69	0.69	0.69
Total liabilities	5.97	7.76	7.53	18.85	20.38	23.05
TOTAL LIABILITIES	**12.05**	**14.51**	**14.3**	**22.68**	**23.94**	**25.2**

Statement of Cash Flows – Main Aggregate

31/12 (m€)	2021	2022	2023E	2024E	2025E	2026E
Earnings	0.37	-0.05	2.43	-0.38	-0.01	3.81
Cashflow	-0.16	-0.03	3.9	0.73	4.7	6.93
Capital expenditure	-0.28	-0.32	-0.43	-0.64	-0.88	-1.22
Impact of working capital requi	-0.04	11.57	-3.91	-2.67	-3.22	-4.83
Free cashflow	-0.48	11.23	-0.44	-2.58	0.6	0.87

Financial ratios

31/12 (€m)	2021	2022	2023E	2024E	2025E	2026E
EPS (€)	**0.02**	**0.05**	**-0.02**	**0**	**0.24**	**0.32**
Market capitalisation (€m)	45.12	45.12	45.12	45.12	45.12	45.12
Enterprise value	20.77	91.29	91.37	93.49	96.42	97.1
P/E	-59.96	122.4	54.12	-120.06	-3949.46	11.83
EV/Sales	3.31	10.43	16.28	14.83	11.32	7.62
EV/Ebitda	24.96	34.11	183.49	95.62	47.99	37.85
EV/Ebit	474.56	43.15	-139.05	-319.21	27.28	19.58
Cashflow/Sales	-0.07	-0.14	0.33	-0.24	-0.15	0.18
Ebit/Sales	0.01	0.24	-0.12	-0.05	0.41	0.39
Net earnings/Sales	0.06	0.28	-0.07	0	0.45	0.41
Gearing	0.23	0.14	-0.09	0.04	0.06	0.05

13 Important warnings

Setting In Extenso Financing & Market Opinions & Price Targets

The opinions mentioned by In Extenso Financement & Marché reflect the absolute performance expected, over a horizon of between 6 and 12 months, for each security considered, in local currency.

1. Strong Purchase	The stock should achieve an absolute return of more than +25%
2. Purchase	The stock is expected to achieve an absolute return of between +10% and +25%
3. Neutral	The stock is expected to move between +10% and -10%
4. Sale	The stock is expected to achieve an absolute underperformance of between -10% and -25%
5. Strong Sale	The stock is expected to achieve an absolute underperformance of more than -25%

Details of the methods applied by In Extenso Financement & Marché to determine its price targets are available on the website www.genesta-finance.com.

Detection of potential conflicts of interest

Participation of the analyst, In Extenso and/or its employees in the issuer's capital	Issuer's participation in In Extenso	Other material financial interests between the issuer and In Extenso	Existence of a market maker or liquidity provider contract between the issuer and In Extenso	Remuneration of In Extenso by the issuer for the preparation of this financial analysis	Remuneration of In Extenso by the issuer for services other than the preparation of this financial analysis	Communication of the financial analysis to the issuer prior to its publication
No	No	No	No	Yes	No	No

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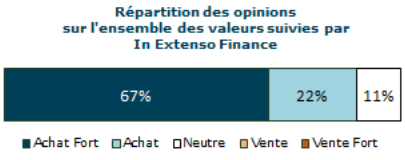
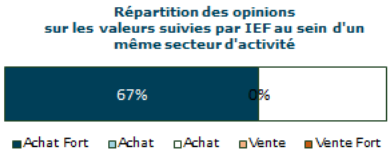
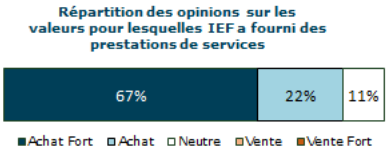
History of value opinions and price targets over the past 12 months

Date	Opinion	Course Objective
June 26th, 2024	Coverage initiation	**€6.01**

Distribution of opinions







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