PART 5

GLOSSARY & BIBLIOGRAPHY

GLOSSARY

Assay	In the field of diagnostics, an assay is a process or method aimed at determining the presence or amount (quantitative assay) of a certain substance in a sample.
Application	In the context of the Idylla™ platform, an application is a specific Nucleic Acid detection assay (test) that is to run on the system. Applications have their own specific requirements.
Batch Record	The set of records of all relevant process information in any physical or electronic format.
Biopsy (solid/liquid)	The Idylla™ platform is capable of processing both solid biopsies (FFPE tissue which is the standard tissue type for solid tumor diagnostics, and fresh (frozen) tissue samples) and liquid biopsies. These are easier to obtain sample types such as blood plasma or urine. Liquid biopsy based assays will facilitate monitoring of treatments and disease progression, and possible earlier disease detection.
Serine/threonine-protein kinase B-raf (BRAF)	BRAF is a protein that, in humans, is encoded by the BRAF gene. The BRAF protein is involved in sending signals within cells and in cell growth. Certain inherited BRAF mutations cause birth defects. Alternatively, other acquired mutations in adults may cause cancer.
CE-mark	The CE-mark is a mandatory conformance mark on many products placed on the market in the European Union. With the CE-marking on a product, the manufacturer ensures that the product is in conformity with the essential requirements of the applicable European Union directives. The letters "CE" stand for 'Conformité Européenne' ('European Conformity').
Clinical data	Safety and/or performance information that are generated from the clinical use of a medical device.
Companion Diagnostics (CDx)	CDx is a bio-analytical method designed to assess: (i) whether or not a patient will respond favorably to a specific medical treatment; (ii) what the optimal dose is for a patient; and (iii) whether the patient can expect certain side effects from a medical treatment. Any prescription of a drug with a CDx is based on the outcome of the CDx. CDx tests are also used in the drug development process.
CLIA	The Clinical Laboratory Improvement Amendments of 1988 (CLIA) regulations include federal standards applicable to all U.S. facilities or sites that test human specimens for health assessment or to diagnose, prevent, or treat disease (source: https://wwwn.cdc.gov/clia/).
Consumables	Materials that are in direct or indirect contact with final product.
COVID-19	In 2019, a new coronavirus was identified as the cause of a disease outbreak that originated in China. The virus is now known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease it causes is called coronavirus disease 2019 (COVID-19) (source: mayoclinic.org).
ctDNA	This is circulating tumor DNA.
Deoxyribonucleic acid (DNA)	DNA is a nucleic acid molecule that contains the genetic instructions used in the development and functioning of living organisms.
Distributor	Person or legal entity that furthers the marketing and/or selling of a device from the original place of manufacture to the ultimate user without modifying the device, its packaging or its labelling.
Epidermal growth factor receptor (EGFR)	EGFR is a protein found on the surface of certain cells which can cause them to divide. It is found in abnormally high levels on the surface of many types of cancer cells.

Emergency Use Authorization (EUA)	This is an authorization given by the FDA Commissioner pursuant to section 564 of the US Federal Food, Drug, and Cosmetic Act, as amended (the 'FD&C Act'), which allows unapproved medical products or unapproved uses of approved medical products to be used in the United States in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by chemical, biological, radiological or nuclear threat agents when there are no adequate, approved, and available alternatives.
Export or distributor markets	Defined as the world excluding European direct markets, US, China and Japan.
US Food and Drug Administration (FDA)	The FDA is a federal agency of the United States Department of Health and Human Services responsible for protecting and promoting public health through the regulation and supervision of, among other things, medical devices.
Formalin fixed, paraffin embedded (FFPE)	FFPE tissues are samples, typically from suspected tumors, that are fixed or mixed with formalin to preserve the structural integrity of the sample. The sample is then embedded into a type of paraffin wax so that it can be sliced into very fine slices, 5-10 microns thick. Treating samples in this manner enables the samples to be stained with dyes to analyze abnormalities in tissue that is suspected of cancer.
Gene signature	RNA expression or gene signature tests are particularly interesting since these often have a high market value. These are based on the differential mRNA expression levels that are calculated into a clinically meaningful score, namely the 'signature' that guides patient management decisions.
ICU	Intensive Care Unit.
Idylla™ Platform	Combination of the Idylla™ Instrument (hardware and software) and the Idylla™ Console (hardware and software) using the Idylla™ cartridge technology.
Idylla™ Cartridge	Refers to the disposable container containing the necessary reagents to perform a Test with the System.
Immunoassay	Immunoassays are assays that measure biomarkers through antigen-antibody interaction technologies. In most cases such assays are used to measure biomarkers of the immune system itself, e.g. HCV or HIV antibodies produced by the bodies, which are detected by means of HCV or HIV antigens.
Influenza	Also known as 'the flu' is a highly contagious respiratory tract infection caused by the family of influenza viruses.
In vitro diagnostics or In vitro diagnosis (IVD)	IVD is a diagnostic test outside of a living body in contrast to "in vivo", in which tests are conducted in a living body (for example an X-ray or CT-scan).
Investigational Use Only (IUO)	An Investigational Use Only (IUO) product is an IVD product, in the testing phase of product development that is being shipped or delivered for product testing prior to full commercial marketing.
Kirsten rat sarcoma-2 virus oncogene (KRAS)	KRAS is a protein that, in humans, is encoded by the KRAS gene. Like other members of the Ras family, the KRAS protein is a GTPase (a large family of hydrolase enzymes that can bind and hydrolyse guanosine triphosphate), and is an early player in many signal transduction pathways. The protein product of the normal KRAS gene performs an essential function in normal tissue signalling, and the mutation of a KRAS gene is associated with the development of many cancers.
KOL	Key Opinion Leader.
Manufacturer	Natural or legal person responsible for the design, manufacture, fabrication, assembly, packaging or labelling of a medical device, for assembling a system, or adapting a medical device before it is placed on the market and/or put into service, regardless of whether these operations are carried out by that person or on their behalf by a third party.

MDSAP (Medical Device Single Audit Program)	The MDSAP allows medical device manufacturers can be audited once for compliance with the standard and regulatory requirements of up to five different medical device markets: Australia, Brazil, Canada, Japan and the United States. The program's main mission is to "...jointly leverage regulatory resources to manage an efficient, effective, and sustainable single audit program focused on the oversight of medical device manufacturers."
Medical Device	Any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of diagnosis, prevention, monitoring, treatment or alleviation of disease, diagnosis, monitoring, treatment, alleviation of or compensation for an injury, investigation, replacement, modification, or support of the anatomy or of a physiological process, supporting or sustaining life, control of conception, disinfection of medical devices, providing information for medical purposes by means of in vitro examination of specimens derived from the human body, and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.
Metastatic Colorectal Cancer (mCRC)	Colorectal Cancer (CRC) is the second most common cancer worldwide, with an estimated incidence of more than 1.36 million new cases annually. According to the International Agency for Research on Cancer, an estimated 694,000 deaths from CRC occur worldwide every year, accounting for 8.5% of all cancer deaths and making it the fourth most common cause of death from cancer.
Molecular diagnostics (MDx)	MDx is a form of diagnostic testing used to detect specific sequences in DNA or RNA that may or may not be associated with disease. Clinical applications of MDx include infectious disease testing, oncology, pharmacogenomics and genetic disease screening.
Micro satellite instability (MSI)	MSI is a genetic hyper-mutability condition resulting from MMR that is functioning abnormally.
Multiplexing	The simultaneous detection of more than one analyte or biomarker from a single sample.
Neuroblastoma RAS viral (v-ras) oncogene (NRAS)	NRAS is a protein that is encoded, in humans, by the NRAS gene. Like other members of the Ras family, the NRAS protein is a GTPase (a large family of hydrolase enzymes that can bind and hydrolyse guanosine triphosphate), and is an early player in many signal transduction pathways. The protein product of the normal NRAS gene performs an essential function in normal tissue signaling, and the mutation of a NRAS gene is associated with the development of many cancers.
Next-Generation Sequencing (NGS)	Sequencing is the process of determining the precise order of nucleotides within a DNA molecule. It includes any method or technology that is used to determine the order of the four bases—adenine, guanine, cytosine, and thymine—in a strand of DNA. The high demand for low-cost sequencing has driven the development of high-throughput sequencing technologies that parallelize the sequencing process, producing thousands or millions of sequences concurrently. High-throughput sequencing technologies are intended to lower the cost of DNA sequencing beyond what is possible with standard dye-terminator methods.
Performance study	Performance study means a study undertaken to establish or confirm the analytical or clinical performance of a device.
Polymerase chain reaction (PCR)	The specific and exponential amplification of DNA sequences by consecutive thermal cycling steps. Real-time PCR is a form of PCR whereby the amplified sequences are made visible by means of fluorescent labelling in real time, i.e., as they become synthesized. Real-time PCR can be used to estimate the quantity of target DNA sequences in a multiplexed way. PCR and real-time PCR can also be used to detect and quantify RNA sequences after a DNA copy has been made from the RNA sequence by means of a reverse transcriptase enzyme.
Protein	Polypeptide chain built from the 20 natural amino acids. Proteins are synthesized from a messenger RNA copy of a gene and can have many functions in the cytoskeleton of the cell, enzymatic, messenger functions in cells and blood such as immune cytokines, DNA binding proteins that regulate ex-pression, etc.

Prototype	(First) materialization of the intended product.
Regulatory authority	A government agency or other entity that exercises a legal right to control the use or sale of medical devices within its jurisdiction, and can take legal action to ensure that medical devices marketed within its jurisdiction comply with legal requirements.
Respiratory Syncytial Virus (RSV)	RSV is a major cause of lower respiratory tract infection that is a frequent infection in children.
Research Use Only (RUO)	This is a category of non-approved (i.e. no CE-marking and FDA approval) medical device products that can solely be used for research purposes. Many producers introduce their products first as RUO and/or IUO products, prior to obtaining 510(k) clearance or PMA approval.
Ribonucleic acid (RNA)	RNA, like DNA, is a nucleic acid molecule. RNAs have a variety of different functions in living cells. They can have a scaffolding role in the build-up of complexes (ribosomes, SNRPs), provide sequence recognition (translation, RNA spicing), have catalytic function (ribozymes), act as messengers for protein synthesis (mRNAs), regulate gene expression (miRNAs) or make up the genome of certain viruses.
SARS-CoV-2	The virus that causes COVID-19.
Screening Test	An initial or preliminary test. Screening tests do not tell you if you definitely have a disease or condition. Rather, positive results indicate that you may need additional tests or a doctor's evaluation to see if you have a particular disease or condition.
Sepsis	Sepsis is a potentially life-threatening condition that occurs when the body's response to an infection damages its own tissues. When the infection-fighting processes turn on the body, they cause organs to function poorly and abnormally. Sepsis may progress to septic shock. This is a dramatic drop in blood pressure that can lead to severe organ problems and death. Early treatment with antibiotics and intravenous fluids improves chances for survival (source: mayoclinic.org).
Serine/threonine-protein kinase B-raf (BRAF)	BRAF is a protein that, in humans, is encoded by the BRAF gene. The BRAF protein is involved in sending signals within cells and in cell growth. Certain inherited BRAF mutations cause birth defects. Alternatively, other acquired mutations in adults may cause cancer.
Stakeholder	Interested party.
White Paper	Customer documentation that explains a specific issue and presents Biocartis standpoint on the matter.

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(2) These linkages are based on a more detailed analysis available on the SDG Compass website: www.sdgcompass.org

(3) Source: https://www.globalreporting.org/standards/

(4) Hummel M. et al, "FACILITATE: a real-world multicentre prospective study investigating the utility of a rapid, fully automated RT-PCR assay vs reference methods (RM) for detecting epidermal growth factor receptor mutations (EGFRm) in NSCLC", ESMO Virtual Congress 2020 (19-21 September 2020), first published online on 14 September 2020

(5) A large, prospective, study across 16 European sites in Belgium, France, Germany and Italy. The study aimed to prospectively test 100 paraffin-embedded biopsy or cytology tissue samples with ≥10% neoplastic cells per site, from patients with advanced NSCLC (non-small cell lung cancer)

(6) Average FTE equals sum of the day-to-day FTE divided by the number of days. This average FTE is calculated on calendar year basis (January-December) and includes all fixed employees, excluding temporary staffing and consultants. The definition has changed versus previous years, where 'average FTE' was calculated including all fixed employees, temporary staffing and consultants

(7) Guangzhou Wondfo Biotech Co., Ltd. ('Wondfo', SHE: 300482)

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(11) Accès aux tests moléculaires EGFR, RAS et BRAF /Résultats d'une enquête dans 5 régions françaises, appui à la décision, INCa, janvier 2016

(12) CAGR = Compound Annual Growth Rate

(13) Source: Research and Markets, Molecular Diagnostics - Global Market Trajectory & Analytics, https://www.researchandmarkets.com/reports/338507/molecular_diagnostics_global_market_trajectory?utm_source=dynamic&utm_medium=GNOM&utm_code=sbdxz7&utm_campaign=1393662+-+Global+Molecular+Diagnostics+Market+Analysis+2020+-+PCR+Technology+Leads+the+MDx+Market&utm_exec=cari18gnomd

(14) Cortes-Ciriano I et al (2017) A molecular portrait of microsatellite instability across multiple cancers. Nat Commun 8: 15180

(15) Zhou et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, published online 9 March 2020, https://doi.org/10.1016/S0140-6736(20)30566-3

(16) Sepsis developed at a median of 9 days (7–13) after illness onset among all patients, followed by ARDS (12 days [8–15]), acute cardiac injury (15 days [10–17]), acute kidney injury (15 days [13–19.5]), and secondary infection (17 days [13–9])

(17) A molecular diagnostics company based in Santiago, Chile

(18) A Palo Alto, CA (USA) based company developing personalized care solutions and targeted therapies for critically ill patients

(19) Developed in collaboration with Immunexpress

(20) In the US, distribution of the Idylla™ SARS-CoV-2 Test was initiated in Q3 2020 per US FDA Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency (Revised), May 2020, Section IV.C. Commercial Manufacturer Development and Distribution of Diagnostic Tests Prior to EUA Submission

(21) Defined as the world excluding European direct markets, US, China and Japan

(22) Excluding instruments returned by Exact Sciences in accordance with the termination agreement announced on 29 October 2020

(23) A companion diagnostic (CDx) test is a test used as a companion to a therapeutic drug, that helps predict if a patient is likely to respond to a treatment or not

(24) Metastatic colorectal cancer

(25) The collaboration was focused on the development of the Oncotype DX Breast Recurrence Score® Test and the Oncotype DX Genomic Prostate Score® (GPS™) Test on the Idylla™ platform. As a result of COVID-19, the project had been suspended earlier during 2020, with the project plan and timing under evaluation. The decision to terminate the agreement was driven by the uncertain timing of a product market release because of the pandemic and a decision by Exact Sciences to shift priorities to other initiatives

(26) ThyroidPrint® is a qRT-PCR (Quantitative Reverse Transcription PCR) based mRNA-expression classifier test (based on RTqPCR analysis, combined with an advanced machine learning algorithm) that helps to determine whether a thyroid nodule with an indeterminate cytology result is benign or malignant (this means that the probability of the nodule being malignant drops from 25% to less than 5%, allowing follow-up to be recommended as an alternative to surgery. Info and source: https://thyroidprint.com/en/home-us/, last consulted on 13 January 2021). A benign test result (NPV or Negative Predictive Value > 95%) allows physicians to recommend watchful waiting as an alternative to diagnostic surgery. This reduces exposing patients to surgical risks and permanent thyroid hormone supplementation. Moreover, it significantly reduces health costs associated with unnecessary surgery. PCR or Polymerase chain reaction is an efficient and cost-effective way to copy (amplify) small segments of DNA or RNA. As such, millions of copies of a section of DNA are made in just a few hours, allowing further analysis for clinicians to diagnose and monitor diseases using a minimal amount of sample, such as blood or tissue. Source: www.genome.gov, last consulted on 13 January 2021

(27) LifeArc, formerly known as the Medical Research Council Technology (MRC Technology, MRCT) is a London (UK) based life science medical research charity

(28) Including research, regulatory oversight, clinical implications, reliability and access

(29) ASCO = American Society of Clinical Oncology, AMP = Association for Molecular Pathology, ESMO = European Society for Medical Oncology, ECP = European Congress of Pathology

(30) Led by researchers from Dartmouth's and Dartmouth-Hitchcock's Norris Cotton Cancer Center (Lebanon, New Hampshire, US). Tsongalis et al., "Comparison of Tissue Molecular Biomarker Testing Turnaround Times and Concordance Between Standard of Care and the Biocartis Idylla Platform in Patients With Colorectal Cancer", Am J Clin Pathol. 2020 Jun 11;aqaa044. doi: 10.1093/ajcp/aqaa044. Online ahead of print

(31) All studies were performed with Idylla™ RUO assays, research use only, not for use in diagnostic procedures. Three studies also discussed new Biocartis assays in the area of infectious disease: the Idylla™ SARS-CoV-2 Assay and the SeptiCyte® RAPID on Idylla™

(32) This represents a major challenge for many current molecular testing methods in a variety of different cancer types

(33) A. Velasco et al., Multi-center real-world comparison of the fully automated Idylla™ microsatellite instability assay with routine molecular methods and immunohistochemistry on formalin-fixed paraffin-embedded tissue of colorectal cancer, Virchows Archiv, https://doi.org/10.1007/s00428-020-02962-x, November 2020

(34) As a result, an aggregate principal amount of EUR 15m of the Bonds was converted, and 1,163,575 new Ordinary Shares were issued by the Company

(35) On 5 April 2017, two new EU regulations on medical devices were adopted: the regulation on medical devices and the regulation on IVD medical devices, both entering into force on 25 May 2017 with a transition period of three years for the regulation on medical devices (May 2020) and five years for the regulation on IVD medical devices (May 2022)

(36) US FDA, https://www.fda.gov/

(37) On 11 July 2017, the US FDA published a final list of devices exempted from 510(k) premarket notification requirements, which included the product code applicable to the Biocartis Idylla™ Instrument and Idylla™ Console. Consequently, Biocartis' Idylla™ Instrument and Idylla™ Console were no longer subject to 510(k) notification requirements prior to being placed on the US market for in vitro diagnostic use with FDA approved or cleared assays. All other US 510(k) requirements, including current Good Manufacturing Practices (cGMP) and vigilance reporting, remain in effect

(38) Source: MedTech Europe, https://www.medtecheurope.org/news-and-events/default/funding-and-reimbursement/

(39) Source: NILA USA, https://www.nila-usa.org/nila/PAMA.asp

(40) Source: Pacific Bridge Medical, https://www.pacificbridgemedical.com/publication/ivd-registration-reimbursement-china/

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[67] PCT = Procalcitonin (PCT) assay is a biomarker for systemic inflammation; CRP = C-reactive protein, a biomarker for systemic inflammation. Positive bacteriological cultures, including blood cultures, may not be available before 24 to 48 hours; interpretation of local colonization may be ambiguous; and traditional markers of infection, such as body temperature and white blood cell (WBC) count, may not be specific

[68] Brazil, Canada, Colombia, Mexico, Saudi Arabia, Spain and Turkey

[69] Quantitative Reverse Transcription PCR. PCR or Polymerase chain reaction is an efficient and cost-effective way to copy (amplify) small segments of DNA or RNA. As such, millions of copies of a section of DNA are made in just a few hours, allowing further analysis for clinicians to diagnose and monitor diseases using a minimal amount of sample, such as blood or tissue. Source: www.genome.gov, last consulted on 22 October 2020

[70] Based on RTqPCR analysis, combined with an advanced machine learning algorithm

[71] This means that the probability of the nodule being malignant drops from 25% to less than 5%, allowing follow-up to be recommended as an alternative to surgery. Info and source: https://thyroidprint.com/en/home-us/, last consulted on 22 October 2020

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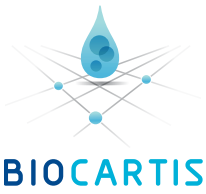
(78) All studies were performed with Idylla™ RUO assays, research use only, not for use in diagnostic procedures. Three studies also discussed new Biocartis assays in the area of infectious disease: the Idylla™ SARS-CoV-2 Assay and the SeptiCyte® RAPID on Idylla™

(79) This represents a major challenge for many current molecular testing methods in a variety of different cancer types

(80) RoHS stands for Restriction of Hazardous Substances. RoHS, also known as Directive 2002/95/EC, originated in the European Union and restricts the use of specific hazardous materials found in electrical and electronic products (known as EEE). Source: www.rohsguide.com

(81) WEEE stands for the Waste of Electrical and Electronic Equipment. The Waste Electrical and Electronic Equipment Directive (WEEE Directive) is the European Community Directive 2012/19/EU on waste electrical and electronic equipment (WEEE) which, together with the RoHS Directive 2011/65/EU, became European Law in February 2003.

(82) REACH stands for Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and is a European Union regulation dated 18 December 2006



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