European Federation of Pharmaceutical Industries and Associations

european biopharmaceutical enterprises

Cancer Biomarkers in the Era of Personalized Medicines

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Definitions

Biomarker[1]	• A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also called a molecular marker and signature molecule.
Companion Diagnostic (CDx)[2]	• A 'companion diagnostic' means a device which is essential for the safe and effective use of a corresponding medicinal product to: (a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or (b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product

1. NCI Dictionary of Cancer Terms: National Cancer Institute Website. https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618. Accessed October 2017.
2. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227

Moving towards Personalized Medicine in Cancer care

Personalized Medicine refers to the tailoring of medical treatment to the individual characteristics of each patient[1]

- **Classify individuals into subpopulations** who differ in their susceptibility to a particular disease or their response to a specific treatment
- Typically, a **diagnostic test is used to assess a biomarker** that helps the physician determine choice of treatment

Personalized Medicine requires:

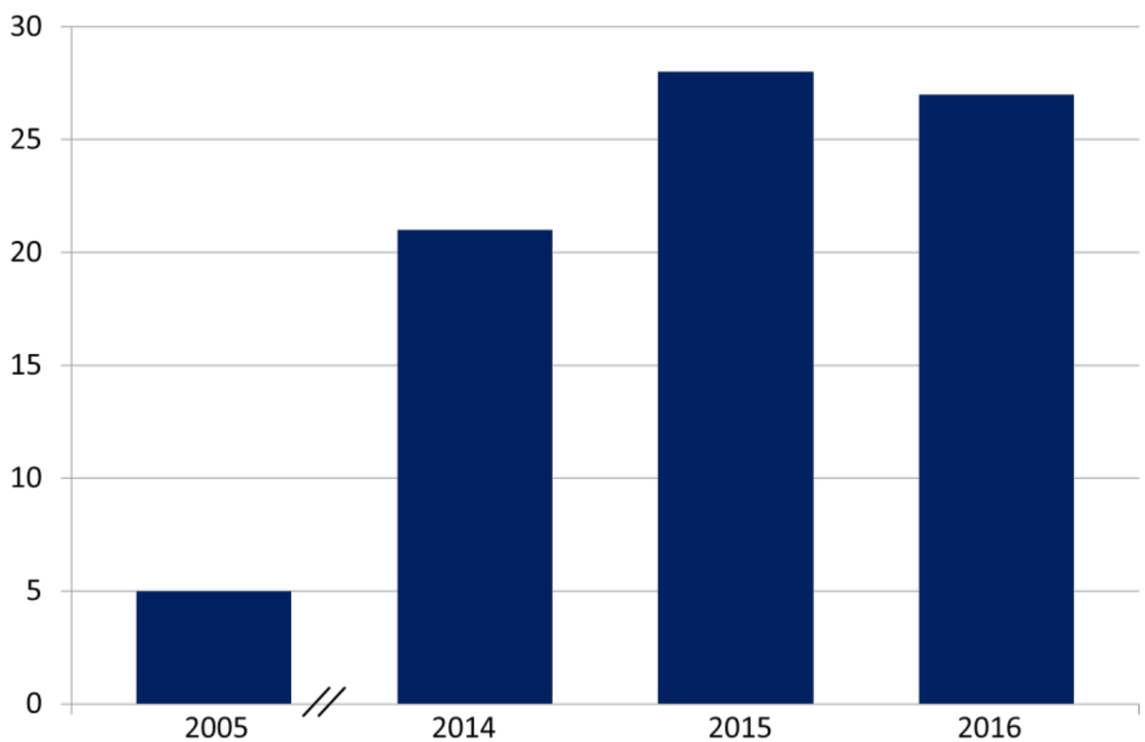
1. A **therapeutic with increased benefit-risk ratio** in a selected patient population, and
2. Development of **reliable and accurate diagnostic test(s)** for patient selection

[1] President's Council of Advisors on Science and Technology "Priorities for Personalized Medicine," 2008.

Personalized Medicine…..by the numbers

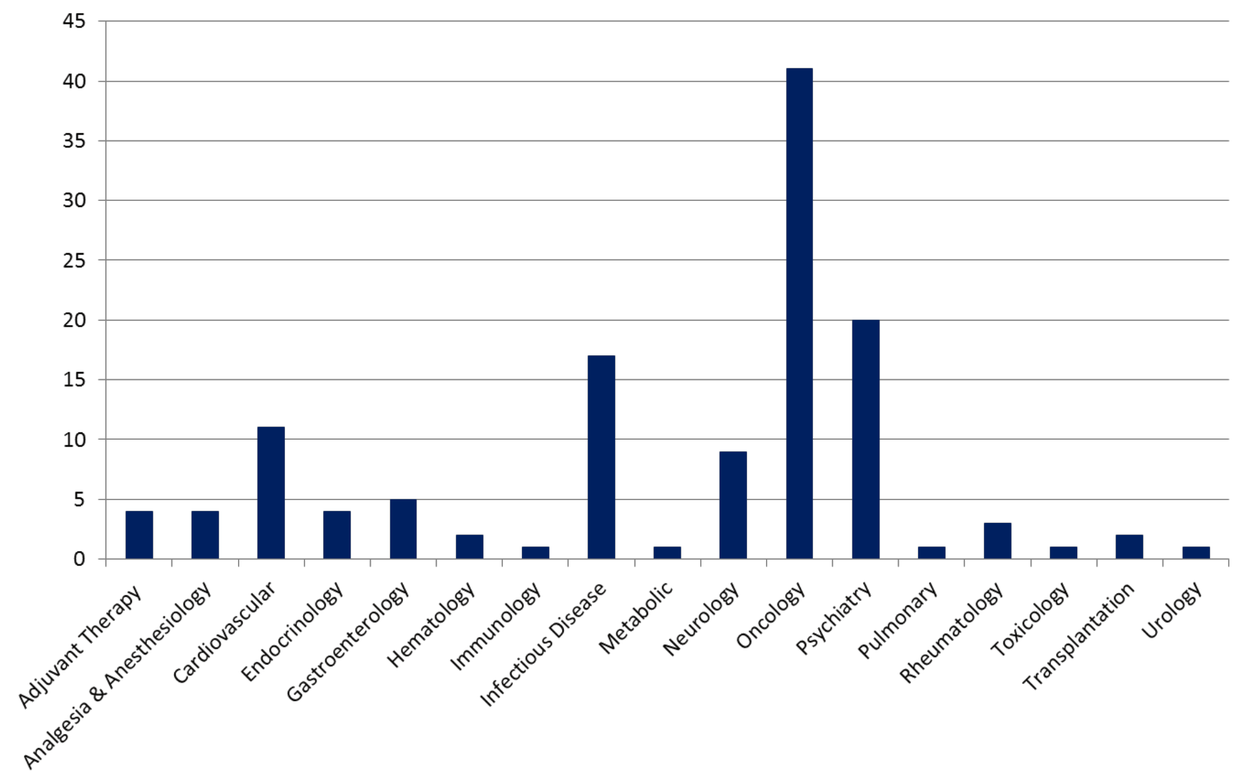
More Than 20 Percent of New Molecular Entities Approved by FDA in Each of Past Three Years are Personalized Medicines[1]

- Up from 5% in 2005
- 50% of the personalized medicines approved by FDA in 2016 are oncology drugs



Approximately 130 medicines include biomarker information in their labels to direct use

- One third in Oncology



[1]Personalized Medicine at FDA: 2016 Progress Report; http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PM-at-FDA.pdf; accessed Apr 2017

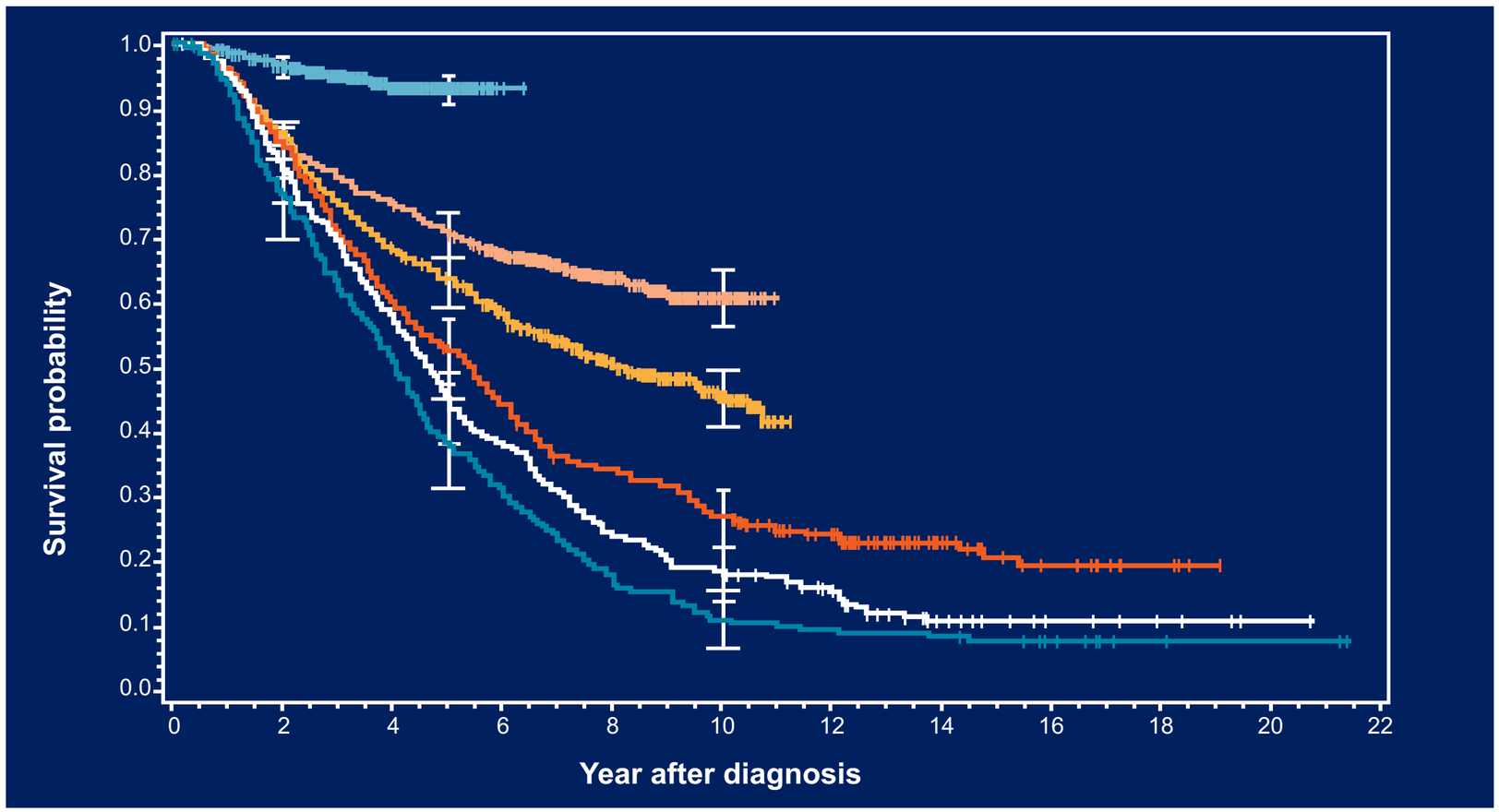
Impact of Personalized Medicine on patients' outcome

Drugs	Indication	Biomarker(s)	Response Rate (%)
Drugs WITH a companion Diagnostic			
Pertuzumab (Perjeta®)	Breast cancer	HER2	**80.2**
Crizotinib (Xalkori®)	NSCLC	*ALK*	**65.0**
Erlotinib (Tarceva®)	NSCLC	*EGFR*	**65.0**
Osimertinib (Tagrisso®)	NSCLC	*EGFR T790M*	**59.0**
Cetuximab (Erbitux®)	Colorectal cancer	EGFR/*KRAS*	**57.0**
Imatinib mesylate (Gleevec®)	GIST	CD117	**53.9**
Dabrafenib (Tafinlar®)	Melanoma	*BRAF*	**52.0**
Vemurafenib (Zelboraf®)	Melanoma	*BRAF*	**48.4**
Ado-trastuzumab emtansine (Kadcyla®)	Breast cancer	HER2	**43.6**
Pembrolizumab (Keytruda®)	NSCLC	PD-L1	**41.0**
Drugs WITHOUT a Companion Diagnostic			
Bevacizumab (Avastin®)	Colorectal cancer	–	45.0
Ixabepilone (Ixempra®)	Breast cancer	–	34.7
Paclitaxel Albumin-bound particles (Abraxane®)	NSCLC	–	33.0
Pemetrexed (Alimta®)	NSCLC	–	27.1
Pembrolizumab (Keytruda®)	Melanoma	–	24.0
Capecitabine (Xeloda®)	Colorectal cancer	–	21.0
Ziv-aflibercept (Zaltrap®)	Colorectal cancer	–	19.8
Eribulin Mesylate (Halaven®)	Breast cancer	–	11.0
Ipilimumab (Yervoy®)	Melanoma	–	10.9
Sunitinib malate (Sutent®)	GIST	–	6.8

Jorgensen JT, et al. Companion diagnostics—a tool to improve pharmacotherapy. Ann Transl Med. 2016;4(24):482.

Impact of Personalized Medicine on patients' outcome

Survival



Imatinib: First therapy targeting BCR-ABL protein (also called Philadelphia Chromosome)

Non specific therapy

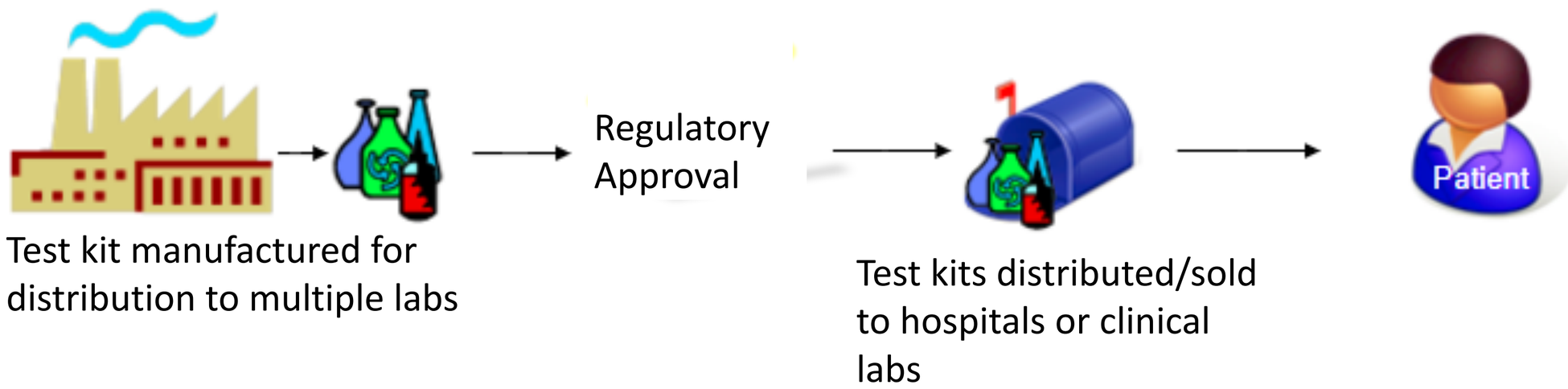
Defining clinical target with CDx drastically improved patient's outcome in Chronic Myeloid Leukemia (CML)

Adapted from R. Hehlmann, German CML Study Group.

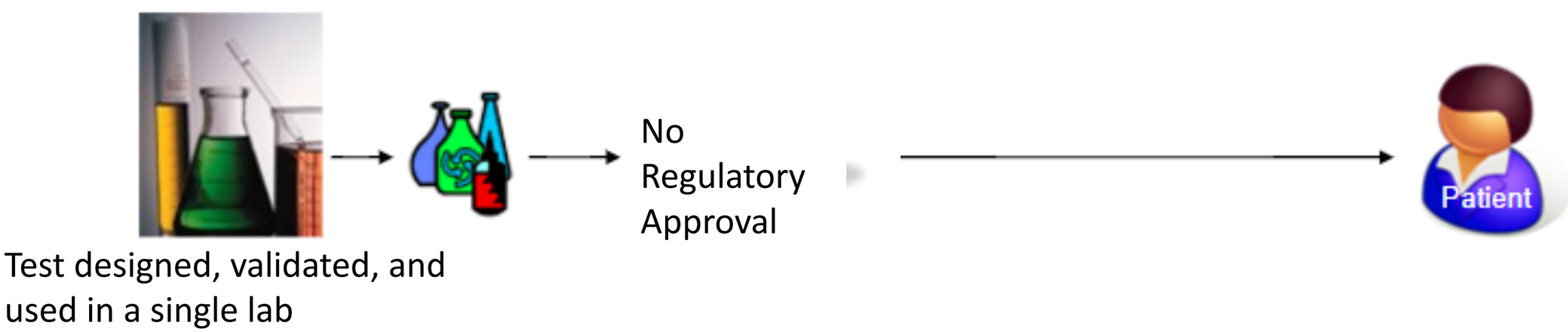
CDx overview: IVD vs IH

In Vitro Diagnostics (IVD) are those tests that can detect diseases, conditions, or infections, while In-House test (IH)* or "home brews" are a type of IVD developed and used by a single lab to evaluate a biomarker.

1) In Vitro Diagnostic (IVD) Test Pathway



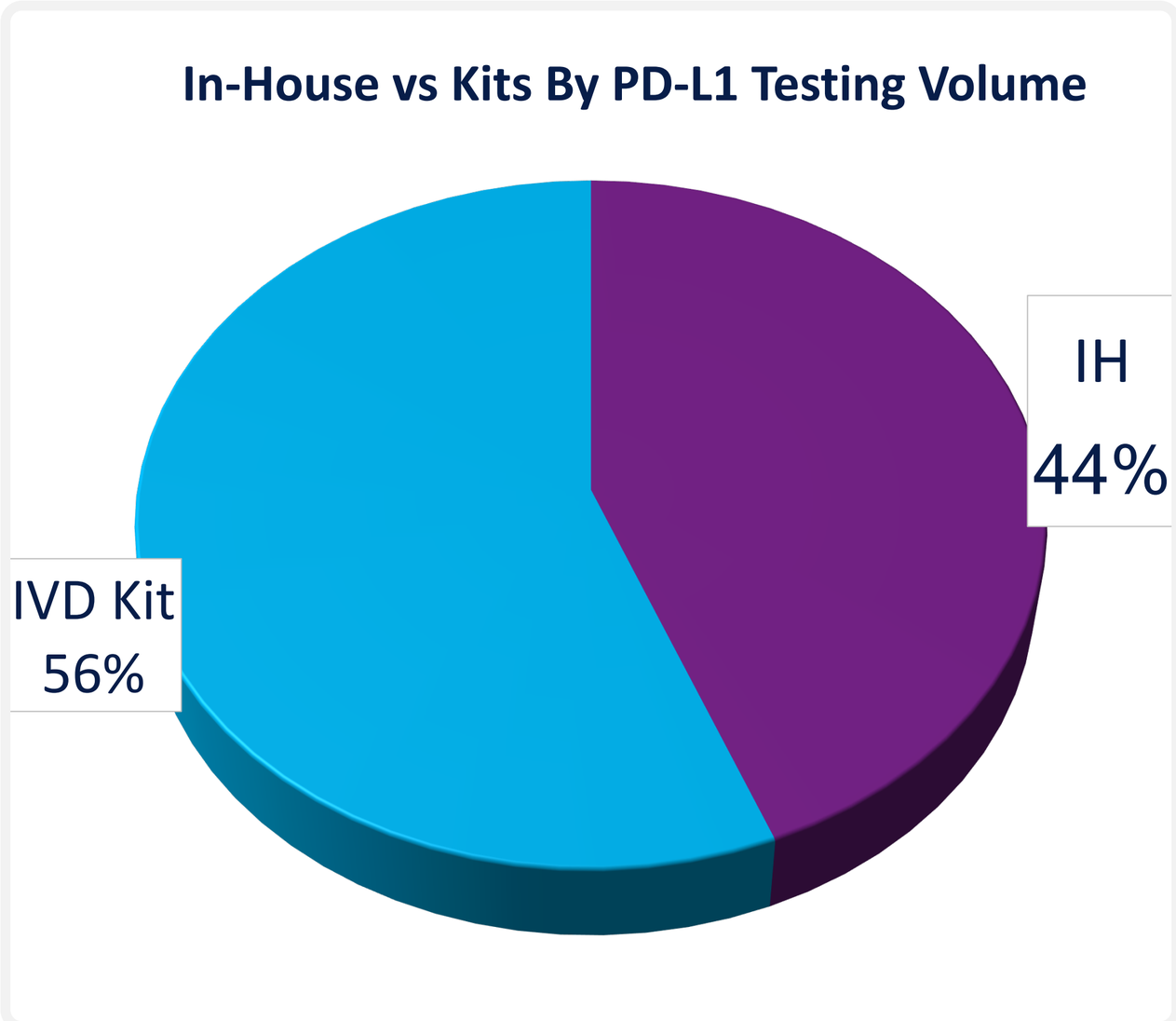
1) In-House (IH) Test Pathway



* Also called Lab developed test (LDT)

CDx overview: Real life practice

PD-L1 kit verses in-House by testing volume shows slight bias towards kit usage:



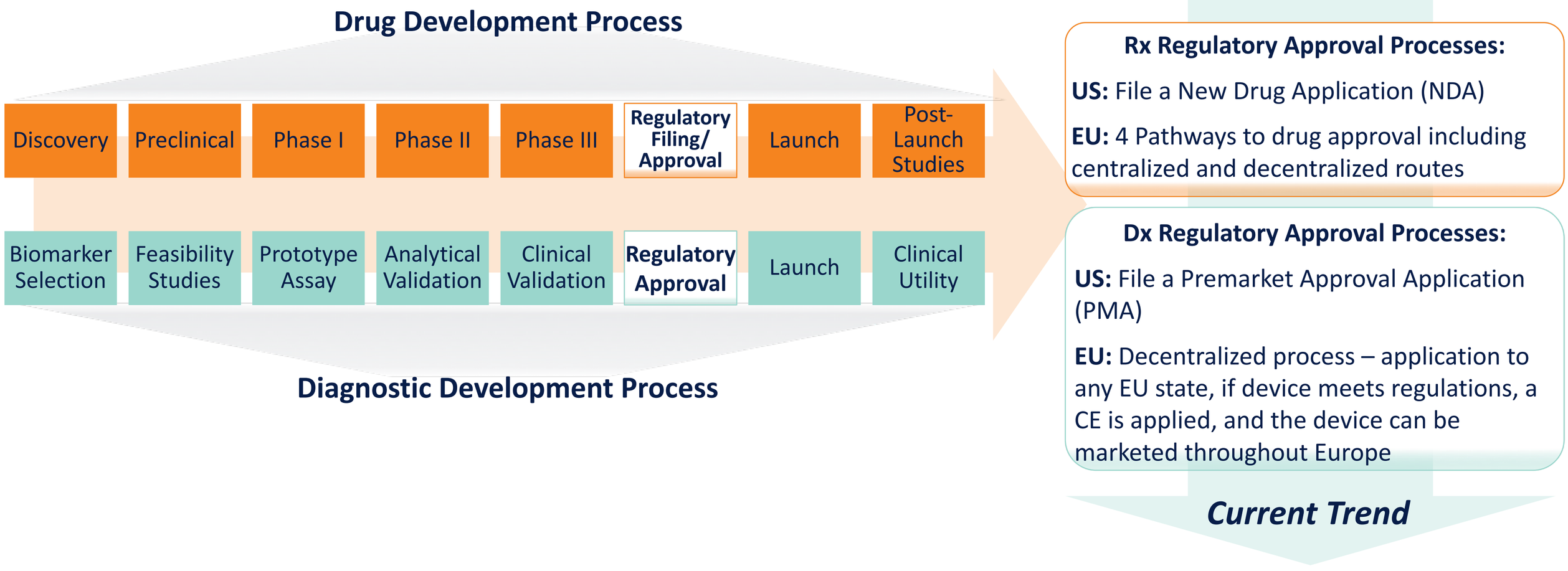
- This chart represents the volume of testing performed in June 2017 for 5 national reference laboratories
- In total this chart represents 4,300 tests performed
- All the labs offer a mix of LDT and Kits

Need to ensure proper CDx testing by establishing testing process, quality check (positivity rate) and standardization (comparison between centers)

PD-L1=Programmed Death Ligand 1.
Data from Diaceutics Laboratory Database.

CDx overview: Regulatory approval

Although the regulatory path to drug and companion diagnostic approval may seem disjointed and complex, efforts are underway to attempt to integrate those parallel processes.



Integrate Regulatory Guidance for CDx

Both the FDA and EMA have recently published draft guidance or a concept paper to begin to address the growing need for more structure regarding co-development of companion diagnostics.

CE=Conformité Européene. EMA=European Medicines Agency. EU=European Union. FDA=Food and Drug Administration.

1. Jorgensen JT, et al. Ann Transl Med. 2016;4(24):482. 2. Van Norman GA. JACC: Basic to Translational Science. 2016;1(5):399-412.

Physician's perspective: Triggers to perform CDx test and challenges

Factors that would encourage physicians to use biomarker tests

Factor	All physicians (n = 895) (%)
Greater availability of biomarker tests where I practice	59
Overall reduction in cost of testing	55
Reduction in time taken to receive results	51
Improved reimbursement conditions for biomarker testing	43
Inclusion in local/hospital guidelines	42
Training for myself (genomics, diagnostic testing, and targeted therapies)	38
Information and tools to help patients understand biomarker testing	34
Other	2
Nothing would help me use biomarker tests more often in my practice	5
Don't know	1

Factors affecting physicians' decision not to perform biomarker tests

Factor	Physicians who do not use biomarker tests (n = 92) (%)
Tests are too expensive/not reimbursed	55
Tests are not available where I practice	47
Not part of treatment guidelines where I practice	35
Results take too long to get	14
I don't want to delay treatment	10
Patients don't want to delay treatment	10
Patients don't understand the benefits	10
The biomarker test does not predict outcome	10
The result of the biomarker test does not influence treatment options	7
Other	2
Don't know	8

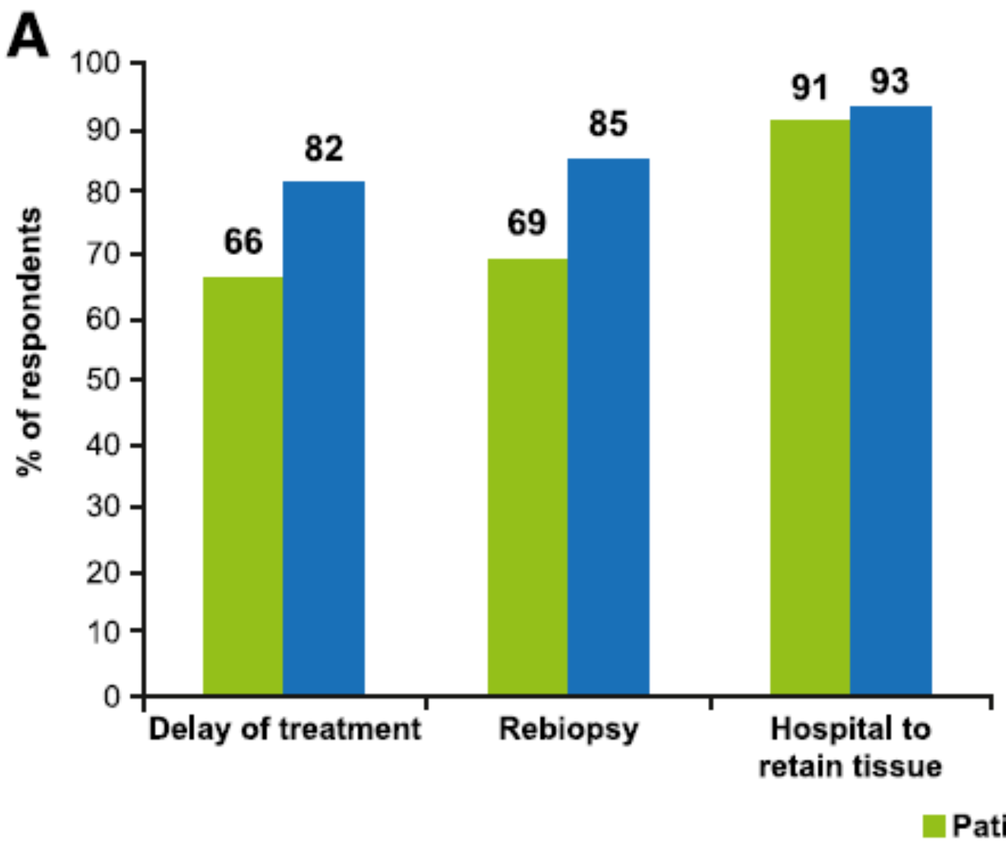
Access and **test funding** are the main challenges

Inclusion of IVD in Local/hospital guidelines is needed for widespread use

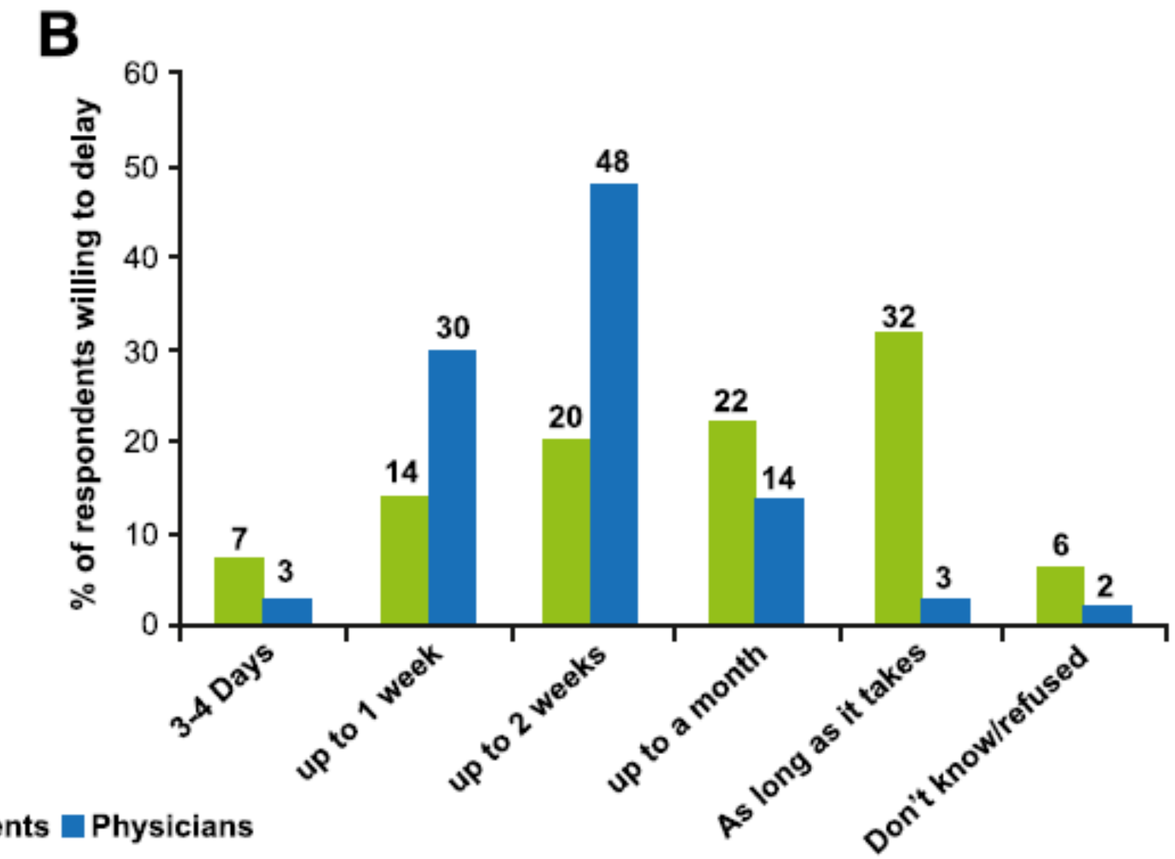
Ciardello et al. Awareness, Understanding, and Adoption of Precision Medicine to Deliver Personalized Treatment for Patients With Cancer: A Multinational Survey Comparison of Physicians and Patients. The Oncologist 2016;21:292–300

Patient's perspective: CDx acceptance

With CDx, will you agree to have….



What is the maximum delay you would accept?



Patients are aware about the role and impact of CDx in treatment decision and would agree to delay treatment initiation

They can accept **longer treatment initiation delay** than physicians

Ciardello et al. Awareness, Understanding, and Adoption of Precision Medicine to Deliver Personalized Treatment for Patients With Cancer: A Multinational Survey Comparison of Physicians and Patients. The Oncologist 2016;21:292–300

Conclusion

CDx transformed the way we treat cancer

- Efficacy and outcome significantly improved
- Impact on the disease journey and time to treatment initiation: Test to be performed prior initiation, patient's follow up , new actor (laboratory)
- Enhance physicians, patients and patients group awareness

CDx regulatory approval and guidelines

- Diagnostic and development process should be undertaken in parallel
- Enhancement and integration of regulatory guidance on CDx assessment and approval pathways*
- CDx to be integrated in International and local clinical guidelines
- In-House test harmonization: Establish process, quality check (positivity rate) and standardization (comparison between centres)

Unlock hurdles for widespread CDx use

- Access: and funding: Establish locally suitable testing pathway so that patients can access the testing, supported by education, training, funding mechanism

Past cancer treatment: One drug for one cancer
Current and future treatment:
The right drug with the right CDx test for the right patient

*Adopted on April 5th 2017: In Vitro Diagnostic medical devices Directive becomes IVD medical devices Regulation 2017/746. Apply after a transition period of 5 years (spring 2022)