Companion diagnostics (CDx) and payment mechanisms

CEE HPN Oncology Event
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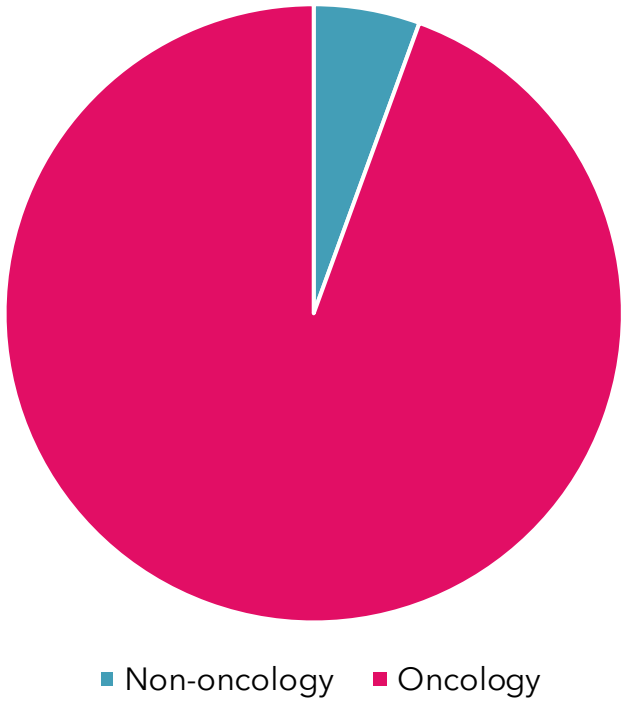
Companion diagnostics (CDx)

- In layman terms – a CDx diagnostic device, a tool of precision medicine, is a test that allows us to prescribe and administer drugs only to people most likely to benefit from them.
- Typically, they detect specific genetic aberrations in patient's tumours based on tissue or liquid biopsy.
- Dako/Agilent Technologies - the first manufacturer to develop a companion diagnostic assay, which was approved by the FDA 25 years ago
- HercepTest - developed for trastuzumab (Herceptin) for the treatment of HER2-positive metastatic breast cancer patients.
- Ideally, CDx test should lead to both better clinical (e.g. higher ORR) and economical (precision medicine) outcomes.
- Historically, CDx have been tied to oncology, although now spreading across drug indications.

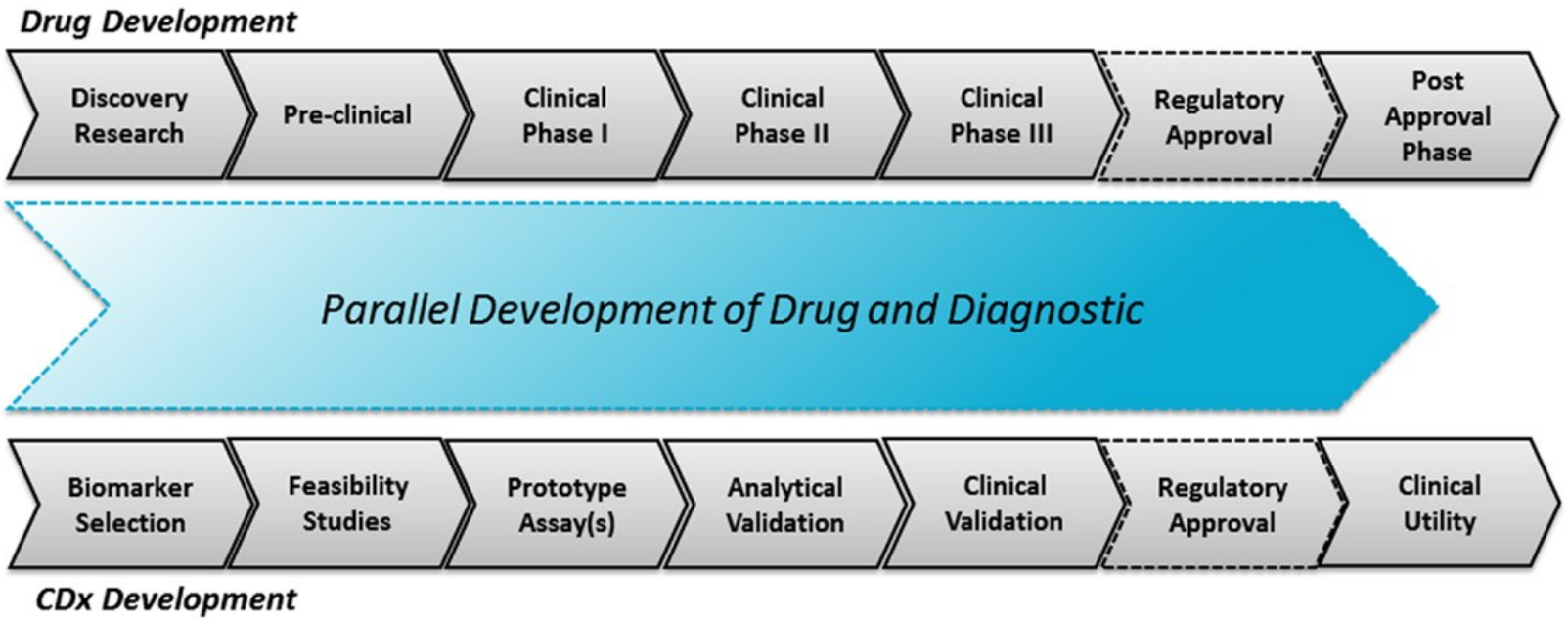
FDA CDx statistics (2023)

FDA approved CDx tests by disease area as of 2023 n=54



Source: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

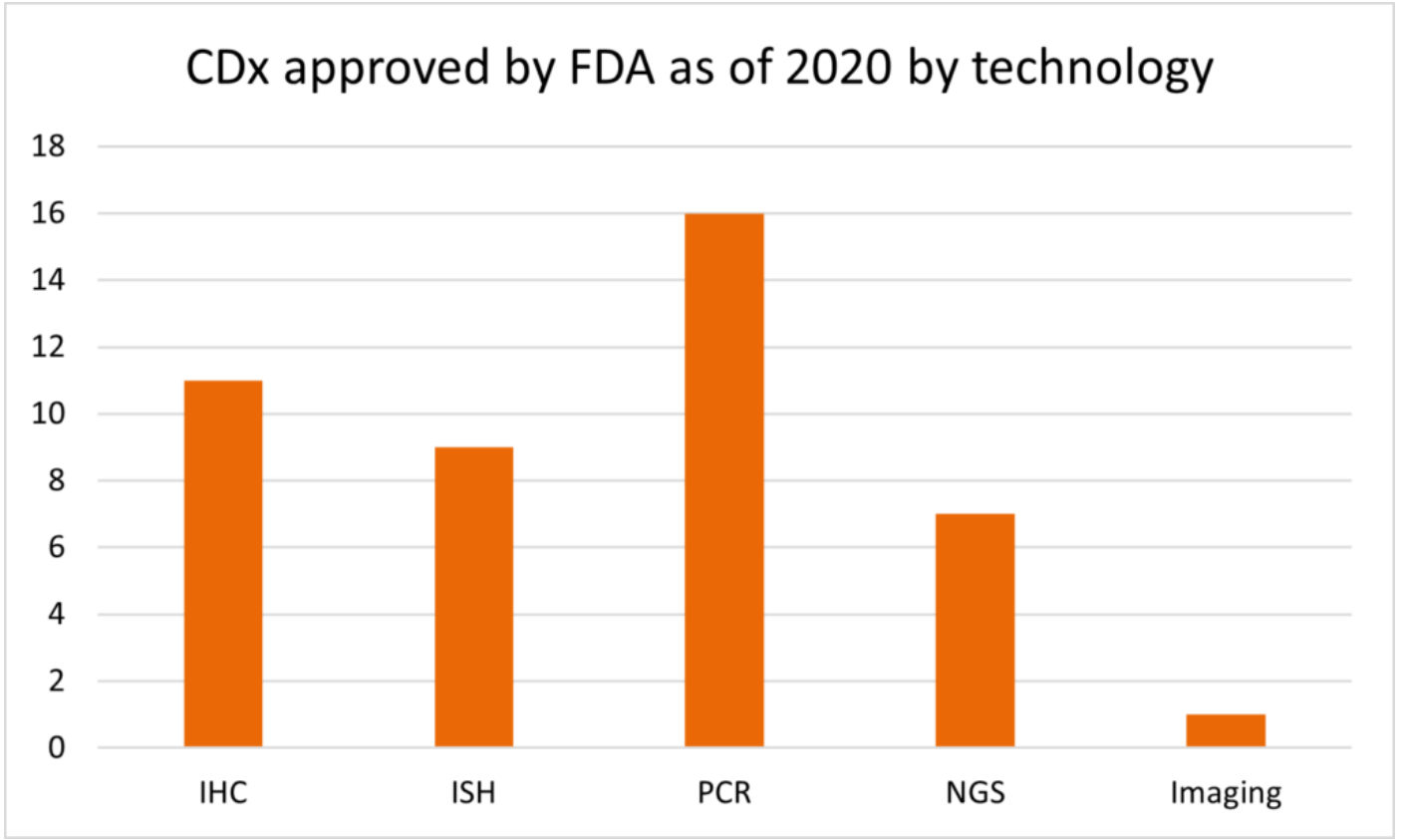
Drug-diagnostic development



- CDx-in-development is typically utilized as a clinical trial assay (CTA) for optimizing patient enrollment in the respective clinical trials as well as for gathering the data necessary for the regulatory approval.

Technology platforms

- Clear trend towards PCR and NGS-based CDx over the past decade(s).
- Immunohistochemis try (IHC) likely to continue play a role.



Source: https://ambiom.com/companion-diagnostics-status-in-2022-and-future-outlook

EU view

Definition of CDx in Europe

Art. 2(7) IVDR

"'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;"

SPC sotosarib:

4.2 Posology and method of administration

Treatment with LUMYKRAS must be initiated by a physician experienced in the use of anticancer medicinal products.

The presence of a *KRAS G12C* mutation must be confirmed using a validated test prior to initiation of LUMYKRAS therapy.

US view

Definition of CDx in the USA

"An IVD companion diagnostic device could be essential for the safe and effective use of a corresponding therapeutic product to:

Identify patients who are most likely to benefit from the therapeutic product

Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product

Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness

Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population"

SPC sotosarib:

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment of locally advanced or metastatic NSCLC with LUMAKRAS based on the presence of *KRAS G12C* mutation in tumor or plasma specimens *[see Clinical Studies (14)]*. If no mutation is detected in a plasma specimen, test tumor tissue.

Information on FDA-approved tests for the detection of *KRAS G12C* mutations is available at: http://www.fda.gov/CompanionDiagnostics.

Regulatory changes

- With the IVDR (EU) 2017/746 coming in force in May 2022, medicines regulatory authorities, including EMA assume a responsibility in reviewing the "suitability" of the CDx in conjuction to the corresponding drug.
- Importantly, CDx devices are now classified as risk class C or even class D devices under IVDR (high patient and public health risk), and must be subject to a conformity assessment carried out by a Notified Body.
- **No more LDTs**. Self-certification by diagnostic companies or commercial laboratories no longer an option. All new companion diagnostic assays introduced in the EU must be CE-marked.

Who pays for this and how?

Reimbursement - Germany

- As of October 2021, 87 drugs required pre-prescription diagnostics in Germany.
- Situation with reimbursement „improved“ over the last years.
- With the Drug Market Strengthening Act 2016 changes introduced; when G-BA (The Federal Joint Committee) issues a statement on the early benefit assessment of the drug, the EBM catalog is adjusted if the product information contains necessary diagnostic test that EBM does not yet have (§ 87 Paragraph 5b Clause 5 SGB V).
- Specifically, regarding oncology; from 1st of July 2016, assays that „*detect certain genetic properties of the tumor and tumor genetic changes*“ are automatically reimbursed prior to administration of the drug. This, however, does not automatically apply to liquid biopsy-based CDx and only applies to ambulatory setting.
- Thomas Seufferlein, President of the German Cancer Society has issued an open letter in 2021 in which he calls for improvement of the reimbursement situation in the stationary care setting.

Reimbursement - Germany

New companion diagnostic tests will be reimbursed via the German Uniform Evaluation Standard (EBM)

31 Aug 2022

On August 11, 2022, the National Association of Statutory Health Insurance Physicians (KBV) announced that two new services in the in-vitro diagnostics field in lung and colon cancer, respectively, will be reimbursed via the German Uniform Evaluation Standard (EBM).

For this purpose, the following new codes for companion diagnostic tests will be included in the EBM catalog:

- 19465 “Detection or exclusion of all known MET exon 14 skipping mutations using circulating tumor DNA to indicate targeted treatment of adult patients with advanced non-small cell lung cancer when mandatory according to the prescribing information” with a tariff of €443.21;
- 32868 “Genotyping to determine UDP-glucuronosyltransferase 1A1 (UGT1A1) metabolization status before systemic therapy with an irinotecan-containing medicinal product” with a tariff of €50.

These changes will be introduced in the EBM catalog on October 1, 2022. The corresponding decisions were made by the Evaluation Committee (Bewertungsausschuss) on August 5, 2022.

The full details in German can be found here and here. The Evaluation Committee decisions can be found here and here.

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Source: https://mtrconsult.com/news/new-companion-diagnostic-tests-will-be-reimbursed-german-uniform-evaluation-standard-ebm

Reimbursement - England

- NICE single/multiple technology appraisal STA/MTA for Rx includes a co-assessment of the drug and CDx. Typical STA time frame 35 – 45 weeks including CDx co-assessment.
- NICE could previously issue a statement on the required parameters the LDT test should fulfil. Orphan indications change the appraisal pathway for Rx but no direct impact on CDx assessment. Innovation by itself not an assessment criterion for CDx tests.
- As of 2018 analyses of a set of 6 most commonly used CDx biomarkers (KRAS, BRAF, KIT…) were being reimbursed through the high-cost procedures list – funded for 3 years from NHS England's budget.
- New test linked to use of a new cancer drug included by NICE within its technology appraisal will be mandated for use across the system when the drug is recommended by NICE (information from 2018).
- Tariffing of medical acts is conducted between local clinical commissioning groups and providers via a tendering process. As a result of tendering at **local level**, variation of tariffs for acts is observed. National Genomic Test Directory for Cancer specifies the genomic tests commissioned by the NHS in England for cancer, the technology by which they are available, and the patients who will be eligible to access to a test.

Reimbursement - Slovakia

- Citing from 363/2011:

363/2011: § 29
(7) For a medical device included in the list of categorized medical devices, a special method of payment for the medical device shall be determined, if it is

a) a medical aid, the provision of which must be performed by the treating medical worker, or

b) an in vitro diagnostic medical device or other medical device intended for the examination or diagnosis of a patient, which must be performed by an attending medical professional.
…"

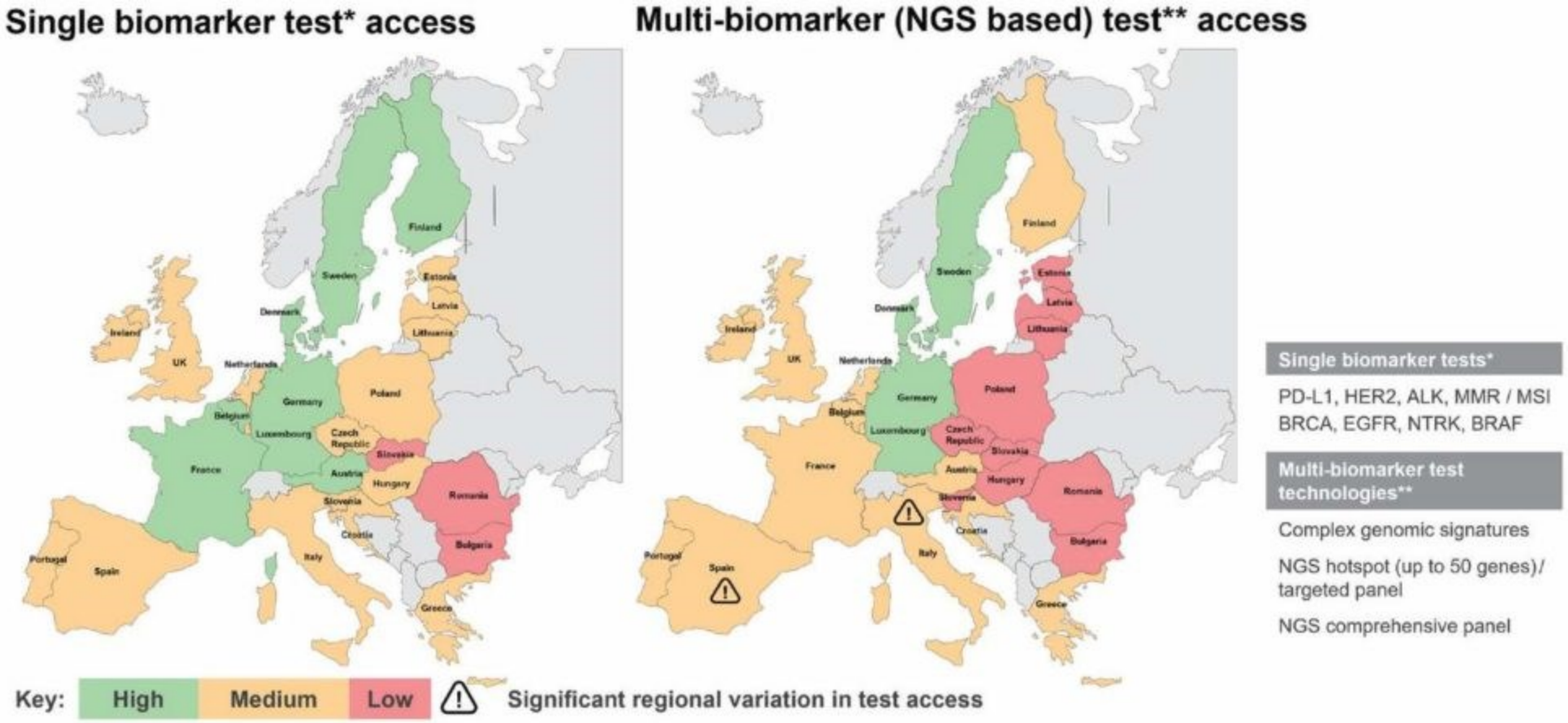
- No mention of approach to CDx reimbursement specifically.

Reimbursement - Slovakia

- From „*Databáza jednotkových nákladov*“; reimbursement of the analysis of HER2 status, BRCA1, BRCA2 full gene sequencing, TP53… significant changes in drug policy and drug inflow, does the list reflect the new reality with more reimbursed drugs?
- The ratio of LDT/CE-marked CDx used?

Issues

- Major variation in predictive rate among different tests and indications, can range from 34% all the way to 90% (80%+ is considered very good).
- Major inter-lab, inter-country, inter-technological variation.
- Resulting difficulties in economic argumentation in front of reimbursement bodies.
- Still lack of experience and suitable project planning among many small-, mid-sized pharma developers.
- As a result many CDx assays do not make it through the regulatory approval or do not even attempt to.



Source: IQNPath, *European Cancer Patient Coalition and* EFPIA *(2021). "Unlocking the potential of precision medicine in Europe – Improving cancer care through broader access to quality biomarker testing".*
NGS indicates next-generation sequencing.

3 takeaways

- Major regulatory changes affecting what can pass as CDx.
- Europe slower in uptake compared to the US.
- Different approaches to reimbursement, Germany leading in Europe.

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