As a cornerstone of the Merck approach to the development of companion diagnostics (CDx), we have developed a CDx guide that is applied across the company to all drug discovery projects. The CDx guide ensures that every project includes a CDx strategy that is fit for purpose and compliant with regulatory requirements. To this end, the CDx guide is built upon the key regulatory CDx documents provided by the US Food and Drug Administration and the Council of the European Union. The guide poses critical questions at each stage of the pipeline, and provides access to the resources needed to address these questions. This approach allows teams to develop innovative CDx strategies with the benefit of expert guidance.

We believe that our approach provides a state-of-the-art model for CDx development. We provide a detailed overview of the Merck CDx guide as a resource and inspiration for other pharmaceutical and biotechnology companies to use in working toward an industry-harmonized standard.
Our understanding of the cellular changes that cause many diseases, including cancer, has grown enormously in recent years. We now know that many diseases, particularly cancer, are caused by changes to the molecules that normally regulate cells and keep them healthy. Targeted drugs can be used to reverse these changes and treat the disease. For example, if a disease is caused by a change in protein X, a drug targeting protein X is likely to work, but not if the disease is caused by a change in an unrelated protein Y. In addition to not working, the wrong drug might cause unwanted adverse effects. Tests are therefore required to determine the underlying molecular cause of a patient’s disease, so that they can be given the correct drug. These tests are termed companion diagnostics. The development of companion diagnostics has to be carefully managed so that they accurately select the appropriate patients for inclusion in drug trials and can then be used to select patients to receive approved drugs. The Food and Drug Administration (FDA) in the USA and the Council of the European Union have each provided guidelines for the development of companion diagnostics. The Merck companion diagnostics guide integrates and builds upon these regulatory documents, prompting our scientists to ask the right questions at the right time as they develop a companion diagnostic. This gives them freedom to innovate within regulatory limits. We believe our companion diagnostics guide makes an important contribution to drug development. Here, we share the essence of our companion diagnostics guide to help the industry.

Merck is committed to the development of novel drugs that bring real benefit to patients. An increasing proportion of Merck’s portfolio consists of agents intended to modulate the activity of specific targets that are aberrantly active in disease. Because such agents are likely to be effective only in patients in whom disease is caused by the aberrant activity of the target, it is imperative that only these patients are treated. It may also be necessary to exclude patients if treatment could cause unacceptable toxicity. Patients can be identified using companion diagnostics (CDx), defined by the US Food and Drug Administration (FDA) as ‘an in vitro diagnostic device (or an imaging tool) that provides information that is essential for the safe and effective use of a corresponding therapeutic product’ [FDA, 2014 #6]. As well as being used to identify patients who are most likely to benefit or are at increased risk for serious adverse events as a result of treatment with a particular therapeutic product, CDx can also be used to monitor response to treatment so that treatment can be adjusted to improve safety or effectiveness.

The need for CDx regulation is recognized by authorities including the FDA and the Council of the European Union. The FDA published guidelines for development of CDx for the pharmaceutical industry in 2014, followed by a practical guide in 2016. The Council of the European Union adopted similar guidance, the in vitro diagnostic devices directive, on February 22, 2017; this started being enforced in June 2017.

Merck recognizes the need to maintain compliance with all relevant regulatory guidelines, and seeks to integrate them seamlessly into the drug development process. Therefore, Merck has developed and implemented the Precision Medicines Initiative (PMI), which is built upon three pillars: 1) identify the right biological target for the selected disease; 2) select the correct drug dose; and 3) identify the right patient group to receive treatment. The Merck CDx guide is an important component of the third pillar, providing the foundation for patient-focused research and development that delivers differentiated, high-value drug candidates to the patient groups who will benefit most from them. The Merck CDx guide is an educational tool and strategic roadmap intended to maximize the readiness and robustness of a CDx program implemented during targeted drug development. To achieve this objective, the CDx guide provides clear practical guidance to project teams, enabling the aspirations of the PMI to be realized effectively and consistently. The guide ensures that a CDx strategy is an integral part of the drug development plan, requiring that appropriate teams of experts are engaged at each step, that appropriate team support is provided, and that CDx-related questions are asked and addressed at the appropriate time. To ensure regulatory compliance, the Merck CDx guide is built upon the FDA CDx guide framework and the in vitro diagnostic devices directive from the Council of the European Union. The Merck CDx guide is a living document that will be updated periodically to reflect changes in Merck processes and the regulatory landscape. The guide cannot and does not seek to prescribe the CDx strategy for each drug project, but rather enables teams to develop their own custom strategy consistent with best practice.

**Principles of the Merck CDx guide**

The first version of the CDx guide was released internally on September 29, 2016, with immediate effect. Version 1.1, incorporating changes to comply with the newly approved in vitro diagnostic devices directive of the Council of the European Union, has been effective since May 8, 2017.

The guide employs a structured question-based approach to foster critical evaluation and creative thinking throughout the drug development process, and applies to both internal projects and collaborations with diagnostic partners. It identifies expert support that can be called upon to help teams answer their CDx questions. As the teams’ strategies progress, CDx management is provided to coordinate multidisciplinary support and to facilitate working with partner companies. The guide thereby ensures that drug delivery teams in Merck can consistently formulate and deliver effective, efficient, and compliant CDx strategies.
Overview of the CDx development process

Delivery of a successful CDx requires completion of three key stages of development: diagnostic assay identification; assay validation; and commercialization (Figure 1). Assay identification occurs as part of the discovery process, when candidate predictive biomarkers of patient response are identified and preliminary biomarker assays are developed. When formal development of CDx is indicated (patient stratification identified as necessary), validation and approval must follow drug development timelines to enable simultaneous regulatory approvals of the CDx and candidate drug. Commercialization requires business, regulatory and legal considerations to be addressed in addition to issues of validity and performance. This starts with identification of the path to market (Box 1). Turnaround time, marker penetration, reimbursement, and education and training of medical professionals must also be considered. Post-approval life cycle management is essentially mandated in the EU, requiring proactive surveys of the scientific and competitive landscape. A risk mitigation plan is developed and maintained at each stage. The FDA CDx guidelines require that CDx delivered alongside a drug demonstrate three key attributes: analytical validity; clinical validity; and clinical utility (Figure 2). Analytical validity establishes that an assay is sufficiently sensitive, accurate, and robust to detect the analyte/biomarker of interest to a level that supports informed clinical decision-making. Clinical validity establishes that the test results are correlated to the clinical outcome measure of interest. This must be established prior to registration studies. Clinical utility is established by showing that the test enables an improved clinical outcome; this is normally required to qualify a test for payer reimbursement, and is required by the FDA in the case of diagnostic assays used to identify patients qualifying for drug treatment.

The Council of the European Union in vitro diagnostic devices directive stipulates different but similar performance indicators: scientific validity; analytical performance; and clinical performance. Scientific validity requires an association to be established between an analyte and a clinical condition or physiological state.

Analytical performance requires a device to correctly detect or measure an analyte, while clinical performance is determined by the ability of a device to yield results that are correlated with a particular clinical condition relevant to the target population.

Regulatory guidelines require that an assay is fit for purpose as it progresses from phase I exploratory biomarker to phase III diagnostic biomarker. In addition, pharmaceutical companies seek to ensure that CDx are delivered in a timely manner to avoid possible delays to the launch of dependent drugs. At earlier, exploratory stages, a lower level of validation may be acceptable because the primary risk is to business outcome, i.e. potential delay to CDx delivery. At later stages, a higher level of validation is necessary because the risk includes patient outcomes, i.e. incorrect selection of patients for treatment. A high-level summary of the critical steps required for the development of CDx is shown in Figure 3.
**Analytical Validation**
- Evidence that test accurately detects analyte of interest
- Assay standardization and performance characteristics
  - Sensitivity, specificity, precision, accuracy, ...

**Clinical Validation**
- Association of test result with clinical outcomes
- Negative predictive value, positive predictive value, cut-off

**Clinical Utility**
- Evidence that use of test results in improved clinical outcome for patient

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**Figure 2.** CDx development occurs in tandem with drug development.

IVD: in vitro diagnostic; IUO: investigational use only; IDE: investigational device exemption; PEO: performance evaluation only

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**Figure 3.** High-level summary of the critical steps required for the successful delivery of CDx.

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*IDE required in case of “significant risk” (SR) as per FDA risk determination
** acc. to EU IVD regulatory framework
*** Quality system & CGMP requirements as per FDA 21 CFR part 820
Considerations affecting the Merck CDx strategy

The Merck CDx strategy is adaptable and pragmatic, taking into account the current scientific, clinical, commercial, and regulatory landscapes. Key considerations are the nature and diversity of biomarkers, the assays available for their measurement, the proposed clinical strategy within which CDx are developed, regulatory requirements, and clinical and commercial considerations. The CDx strategy provides a route from biomarker to verified classifier, enabling successful patient selection. This must accommodate biomarkers that are dichotomous (e.g., wild-type vs mutant), continuous with a cutoff (e.g., serum biomolecule level), or composite (e.g., strength of gene expression signature). For non-dichotomous biomarkers, establishing appropriate cut-offs is critical to balance patient inclusion vs benefit to the population. Regardless of the nature of the biomarker, developed assays must be fit for purpose and adaptable to available technology platforms and reagents.

Throughout clinical development, the CDx development plans must remain in step with the clinical development strategy, e.g., adapting as indications for drug treatment are defined, and meeting timelines should approval be accelerated. CDx plans must factor in clinical and commercial considerations that affect the viability of CDx. The impact of factors affecting CDx distribution, accessibility, and competitiveness of the companion drug must be considered. Compliance with all relevant regulatory requirements must be maintained throughout. Because these factors are subject to change, the CDx guide is necessarily a living document, subject to revision as circumstances dictate.

Elements of the Merck CDx strategy

There are three key functional elements enshrined in the CDx strategy: the risk assessment and mitigation plan; assembly of a cross-functional team; and definition of the target test profile. The risk assessment and mitigation plan ensures that known risks to CDx delivery are identified and mitigation plans put in place (Box 2). The mandated CDx cross-functional team ensures that input from multiple subject matter experts is accessed, coordinated, and processed (Figure 4). Development of in vitro diagnostics is often outsourced to a commercial partner, in which case a joint CDx development team is typically convened. The target test profile is akin to the target product profile of a drug and describes the required performance, market, and regulatory characteristics of the final approved device.

The CDx strategy assesses all of the critical issues that must be addressed to ensure timely co-development of CDx that meet the target test profile and are fit for purpose (Figure 5 and Box 3).

Post-launch activities

The CDx strategy encompasses post-launch activities that ensure successful life-cycle management. We support diagnostic company partners to ensure that the CDx test is available and correctly implemented to support patient selection. This involves the education of patients, physicians, laboratory staff, and pathologists. Additional support for CDx deployment and pharmaceutical company financing of testing to help drive drug adoption may be provided as use increases in countries with more complex diagnostic and treatment challenges. Drug project teams are required to monitor for new scientific insights, new technologies, and shifting market trends, and to develop second-generation CDx where necessary.

Summary and perspectives

The introduction of a formal CDx strategy has signaled a cultural change within Merck. Previously, project CDx strategies were formulated ad hoc. This was inefficient, and risked mistakes that could delay drug launch and be costly to rectify. The CDx guide provides clear, practical guidance and support to drug projects. Our question-based approach allows for innovation while ensuring consistency and compliance with regulatory requirements. The CDx guide is mandatory, and requires greater discipline from drug development programs. Meeting these demands is rewarded by improved performance.

Figure 4. The contributions of the subject matter experts required to deliver the CDx strategy are coordinated by the CDx management team. Green = External Partners Mauve = Company Internal Functions
Figure 5. The CDx strategy prompts drug teams to engage relevant subject matter experts and compile information in a structured, logical manner when constructing a target test profile.

Box 1. Two paths to market for CDx.

CDx may reach the market either as an in vitro diagnostic (IVD) kit or as a laboratory-developed test (LDT). IVD kits are developed and manufactured by diagnostics companies. Approved kits are distributed to competent laboratories, allowing de-centralized testing, and are typically used when patient populations are large. LDTs are analytically validated in a local laboratory and allow centralized testing. Stringent quality standards defined by the Laboratory Improvement Amendments of 1988 are required in the USA [5]. LDTs are typically used when patient numbers are low, when the assay will be unfamiliar to testing laboratories, or when the assay is implemented on a platform that is not widely available.

Box 2. Risks to CDx delivery

Variable specimen characteristics and quality due to the intrinsic biology of the biomarker (e.g. spatial and temporal tumor heterogeneity, or molecular evolution of the tumor over the course of disease) and/or due to specimen collection, handling, and storage (e.g. pre-analytical factors, amount of tumor tissue, or analyte stability).

- Specimen availability for rare indications can limit enrolment (primarily US readers) in clinical trials, availability of commercial samples to be used in validation studies, and availability of source materials for controls.
- Technical issues occurring during assay development (e.g. availability of reagents, design changes, or bridging studies).
- Business risk occurring during assay development (e.g. supplier goes off-market).
- Issues occurring during clinical biomarker validation, including cut-off determination (e.g. strength of the patient selection hypothesis, size of test, and training set or clinical database).
- Changes to the clinical development plan (e.g. accelerated approval strategies, additional indications).
- Changes to Investigational Use Only or changes of the test itself during phase III/pivotal trial.
- Requirements for regulatory approval of the CDx in the markets of interest (e.g. specific requirements for testing of local samples).
- Market access and reimbursement of the CDx (e.g. stakeholder education, substantiation of value).
Box 3. Some examples of key questions to be addressed at each decision point by project teams. More and more detailed questions are included in the CDx guide. Similar questions posed at multiple stages are shown here only once for illustration.

**Decision Point LO**
- Do the characteristics of the target, pathway, and disease suggest a stratified medicine approach may be beneficial?
- Should patients more likely to respond to treatment be ‘ruled in’ or should those with a greater risk of adverse events be ‘ruled out’?
- Do preclinical data supporting the hypothesis exist (in vivo, in vitro), or need to be generated?
- What is the prevalence/variance in expression of the potential predictive biomarkers?
- Is patient stratification justified?
- Is the underlying biology understood in sufficient detail and how can it be further explored?
- Which key factors may contribute to prediction to response considering the complexity of immune system and tumor cell interaction as well as the role of tumor microenvironment?
- Which systematic approaches support further insights into heterogeneity of response?

**Decision Point ED**
- Do new data need to be considered?
- What assays and reagents are available?
- How will assays need to be developed?
- What prevalence/variance in expression do potential predictive biomarkers have?
- What intellectual property is associated with potential biomarkers?
- How can the systematic approaches to gain insights into heterogeneity of response be further refined?
- How could bioinformatics approaches be applied to support this approach?

**Decision Point 0**
- Is the test modality defined?
- Have samples for analytical validation of the assay been identified?
- Are external CDx partners engaged?
- Which quality standards apply?
- What is the plan for interaction with regulatory authorities?
- Are plans suitable for new potential indications?
- Which challenges go along with this approach to understand heterogeneity of response and how can these be addressed?

**Decision Point 1**
- Are biomarker/CDx and Pharma-Diagnostic joint CDx teams established?
- Is assay development running to plan?
- Is a risk assessment and mitigation plan for CDx development available?
- Do clinical plans encompass the CDx strategy?
- Is the CDx strategy up to date, accounting for strategic plans?
- Have commercial implications been considered?
- Are criteria defined for prioritization of the approach to understand heterogeneity of response?
- Which clinical trial designs would meet the specific needs of complex, broad exploratory evaluation of potential contributors to prediction of response (e.g. size of the trial, statistical aspects, subgroup analyses, and expansion arms in multiple specific indications)?
Decision Point 2
- Do plans require updating based on phase I results?
- Will assays be ready for phase II?
- Is a risk assessment and mitigation plan for CDx development available?
- Are all operational aspects of the CDx strategy in hand?
- Have commercial aspects been considered?
- Is the launch plan and expedited access program for the CDx in place?
- Have health economic aspects of the CDx testing been considered?
- Is the drug development program clinically and commercially competitive?
- Which clinical trial designs would meet the specific needs of further exploratory evaluation of potential contributors to prediction of response followed by subsequent conformation (e.g. a “biomarker test phase” followed by a “biomarker confirmatory phase” after an interim analysis)?

Decision Point 3
- Do data from phase II confirm the patient selection hypothesis?
- Has assay development been initiated to ensure availability for phase III?
- Is the launch plan for the CDx driven by the CDx partner set up?
- Are health economic and reimbursement aspects of the CDx testing being considered?

Decision Point 4
- Do data from phase III confirm clinical utility of the proposed patient selection approach?
- Are all regulatory documents for concurrent approval of the CDx by the diagnostic partner available?
- Is a risk assessment and mitigation plan for CDx development available?
- Are activities to support reimbursement of the testing in hand?

Decision Point 5
- Is the CDx approved and available to the market?
- Is a risk assessment and mitigation plan for CDx development available?
- Are activities set up to meet the requirements of post-approval commitments (e.g. in case of accelerated approval based on phase II)?
- Are programs set up to increase awareness of testing need and penetration and quality of testing?
- Are activities set up to support reimbursement of testing?
- Does the CDx strategy reflect revisions to the clinical development strategy, e.g. additional indications/markets?
- Is the patient selection hypothesis relevant to new indications/markets? Is additional work required to test and validate the CDx?
- Have new data from e.g. basic research, competitors’ drug development programs/drugs acting on the same target/pathway (including resistance mechanisms) been considered?

Conduct Phase IV and Manage Life Cycle
- Are activities in place to improve access to testing and test quality?
- Are activities set up to further support reimbursement of testing?
- Are activities for assessment of alternative methods of testing and evaluation of further potential predictive markers set up?
- Is a strategy in place to develop biomarkers particularly for patient selection in phase IV studies?
- Are competitor patient selection approaches for programs/drugs acting on the same target/pathway (including resistance mechanisms) being monitored?
The first version of the CDx guide, based on the FDA guidelines, was rolled out across Merck in late 2016. It has already been revised to accommodate the recently published regulatory requirements of the Council of the European Union. Future revisions will consider feedback from drug projects, changes to regulatory requirements, and advances in technologies to ensure that the strategy remains relevant and effective.

Conflicts of interest
JS, CD, and JS are employees of Merck KGaA, Darmstadt, Germany. AG and DS are employees of EMD Serono, Inc., Billerica, MA, USA, a business of Merck KGaA, Darmstadt, Germany.

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References

Josef Straub, PhD, is a biomedical expert with a strong background in cancer genetics, toxicology, as well as companion diagnostics. After his first degree in Cellular Biology (University of Kaiserslautern, Germany) he got his PhD in inhalation toxicology at the German Cancer Research Center in Heidelberg. Josef was and granted a GSK Junior Research Fellow "Genomics" at Hertford College Oxford where he worked together with Sir Walter Bodmer. He joined the Bayer AG in Wuppertal, Germany where he was in charge of a comprehensive toxicology related profiling effort. After working successfully as an independent consultant in toxicogenomics Josef joined MDxHealth Inc. in Liege, Belgium where he was in charge of R&D and diagnostic development activities in the area of DNA methylation testing. In 2009 Josef joined Merck KGaA where he has been in charge of the clinical Biomarker and Companion diagnostics development program in three different clinical development programs.

Arnold Gelb is Clinical Advisor, Pathology at EMD Serono for strategy and implementation of tissue exploratory biomarkers and companion diagnostics, particularly in immuno-oncology. He is a board certified pathologist who previously has held progressive positions at Halozyne Therapeutics, Quest Diagnostics Clinical Trials and Novartis, and the University of California, San Francisco.

Douglas Sanders received his Ph.D. in Veterinary Pathobiology from the University of Missouri, where he completed a doctoral dissertation and postdoctoral fellowship studying gene and stem cell therapies for rare neurodegenerative diseases and developing biomarker assays to track treatment efficacy. Dr. Sanders subsequently joined the Companion Diagnostics group at Novartis International AG, where he contributed to the development and co-approval
of molecular diagnostic assays in conjunction with oncology therapeutics. Dr. Sanders joined the Clinical Biomarker and Diagnostics group at EMD Serono in June 2016 and is currently working on development of an NGS-based gene expression profiling diagnostic for selection of lymphoma patients and an initiative to standardize liquid biopsy sample collection and strategy across all programs.

Jürgen Scheuenpflug’s professional career/engagement in the field of personalized medicine already started in 2001, when he investigated the toxicological and clinical relevance of N-Acetyltransferase polymorphism within a project granted by the Federal Institute of Risk Assessment Berlin/ Germany.

In Nov. 2014 Juergen has been assigned as Global Head of Clinical Biomarkers & Companion Diagnostics. In this role he is responsible for biomarkers & CDx across therapeutic areas, ranging from Phase I-III including Life Cycle Management. Following his assignment Juergen built-up an Global Immuno-Oncology biomarker & CDx team for JAVELIN, which is an expansive international clinical trial program of the Merck/ Pfizer Alliance exploring the use of PD-L1 inhibition with avelumab to treat multiple types of cancer. Since December 2015 Juergen leads the precision medicine initiative at Merck and is co-chair of the Merck/Illumina collaboration around next-generation sequencing (NGS, oncogene panel). He is member of several joint steering committees with diagnostic partners (e.g. DAKO, Guardant, Molecular MD) and academic collaborators.

Currently, his main focus is to establish smart and efficient biomarker & companion diagnostic strategies in early and late stage immuno-oncology/oncology programs.

Dr. Claudia Dollins received her PhD in Genetics and Genomics from Duke University Medical Center, after which she completed a postdoctoral fellowship at the University of North Carolina, Chapel Hill. Dr. Dollins subsequently joined the US Food and Drug Administration’s Office of In Vitro Diagnostics and Radiological Health as a senior reviewer and later as acting branch chief, gaining experience in the regulatory review practices and policies that govern in vitro diagnostic and companion diagnostic regulatory review. Upon leaving FDA, Dr. Dollins joined Merck KGaA, Darmstadt, Germany, to head the Global Regulatory Affairs, Biomarkers and Diagnostics team.

The Journal of Precision Medicine will be presenting a series of narratives throughout 2018 focusing on how public/private partnerships are propelling Precision Medicine into the clinic. If you have a unique story to tell and you would like to create your own bespoke webinar please contact Christopher Fleming Ph.D Editor- at -Large. CFleming@thejournalofprecisionmedicine.com