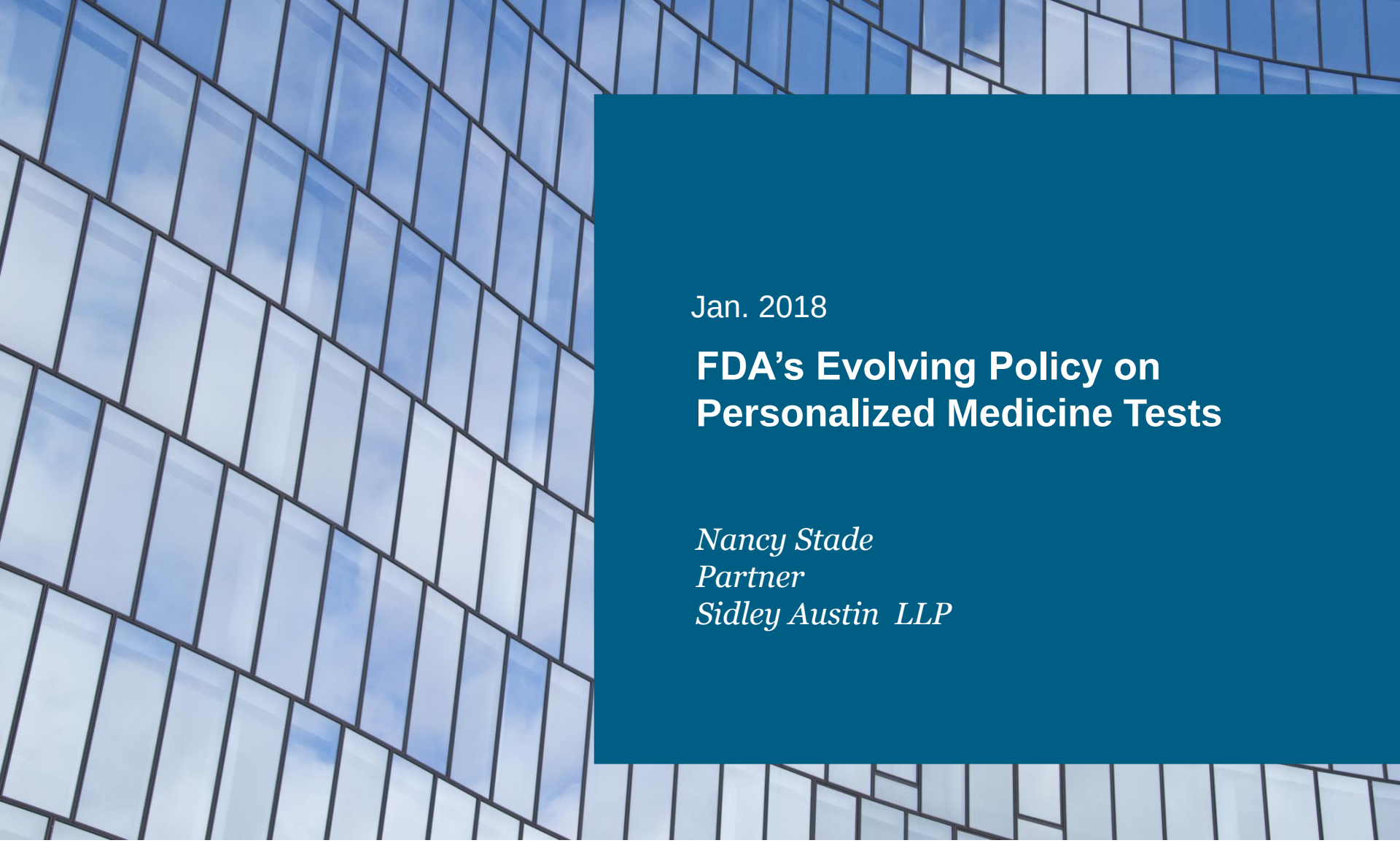

Jan. 2018

FDA's Evolving Policy on Personalized Medicine Tests

Nancy Stade
Partner
Sidley Austin LLP

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150 YEARS

Agenda

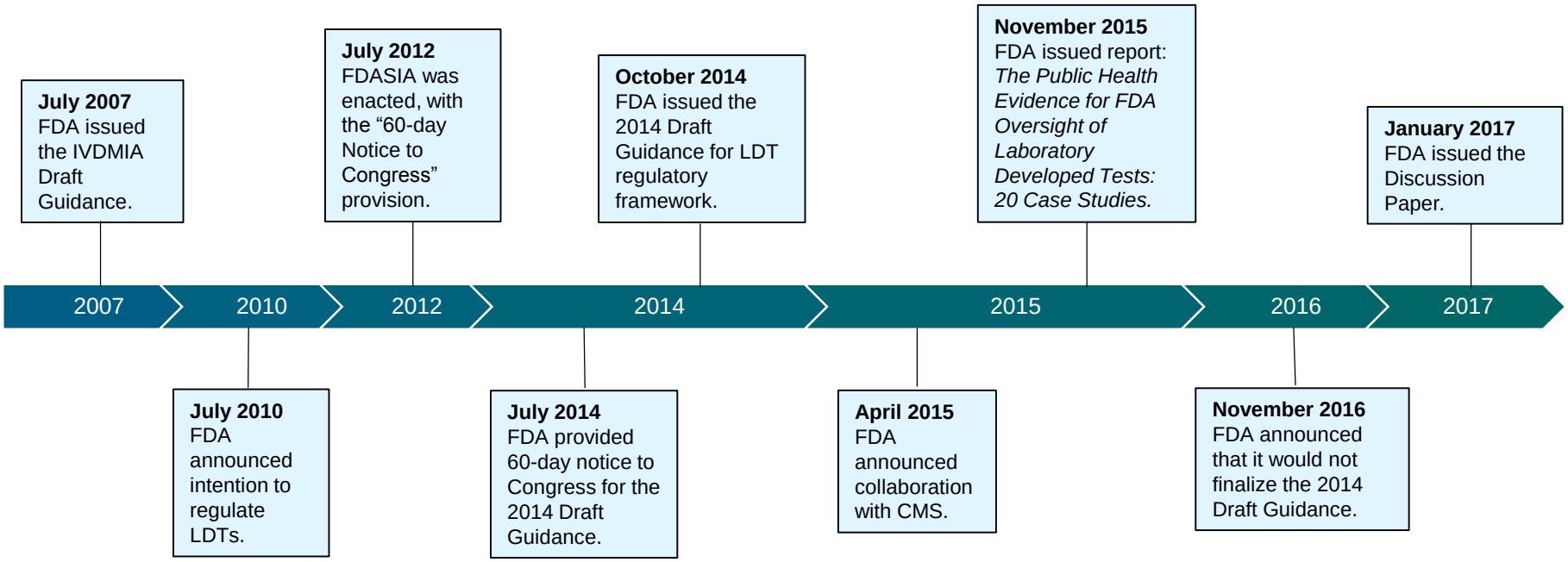
I. Update on Laboratory Developed Tests

II. Direct-to-Consumer Genetic Health Tests

III. Developments in Pharmacogenomics Tests

Update on Laboratory Developed Tests

Recent History of LDT Regulation



2014 Draft Guidance and Its Finalization

- In 2014, FDA released a draft guidance outlining a risk-based framework for regulating LDTs.
- Definition of "LDT": "FDA defines the term *laboratory developed test* (*LDT*) as an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory."
- Feedback: Industry players criticized the framework as being overly burdensome, expensive, and slow. Further, the laboratory and pathologists communities insist that LDTs should only be regulated by the Centers for Medicare & Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA).
- In Nov. 2016, amid post-election uncertainty, FDA decided to delay finalizing the 2014 draft guidance.

"The FDA believes that patients and health care providers need accurate, reliable, and clinically valid tests to make good health care decisions inaccurate or false test results can harm individual patients. We have been working to develop a new oversight policy for laboratory developed tests, one that balances patient protection with continued access and innovation, and realize just how important it is that we continue to work with stakeholders, our new Administration, and Congress to get our approach right. We plan to outline our view of an appropriate risk-based approach in the near future. It is our hope that such an approach will help guide continued discussions."

— An FDA Spokesperson

2017 Discussion Paper

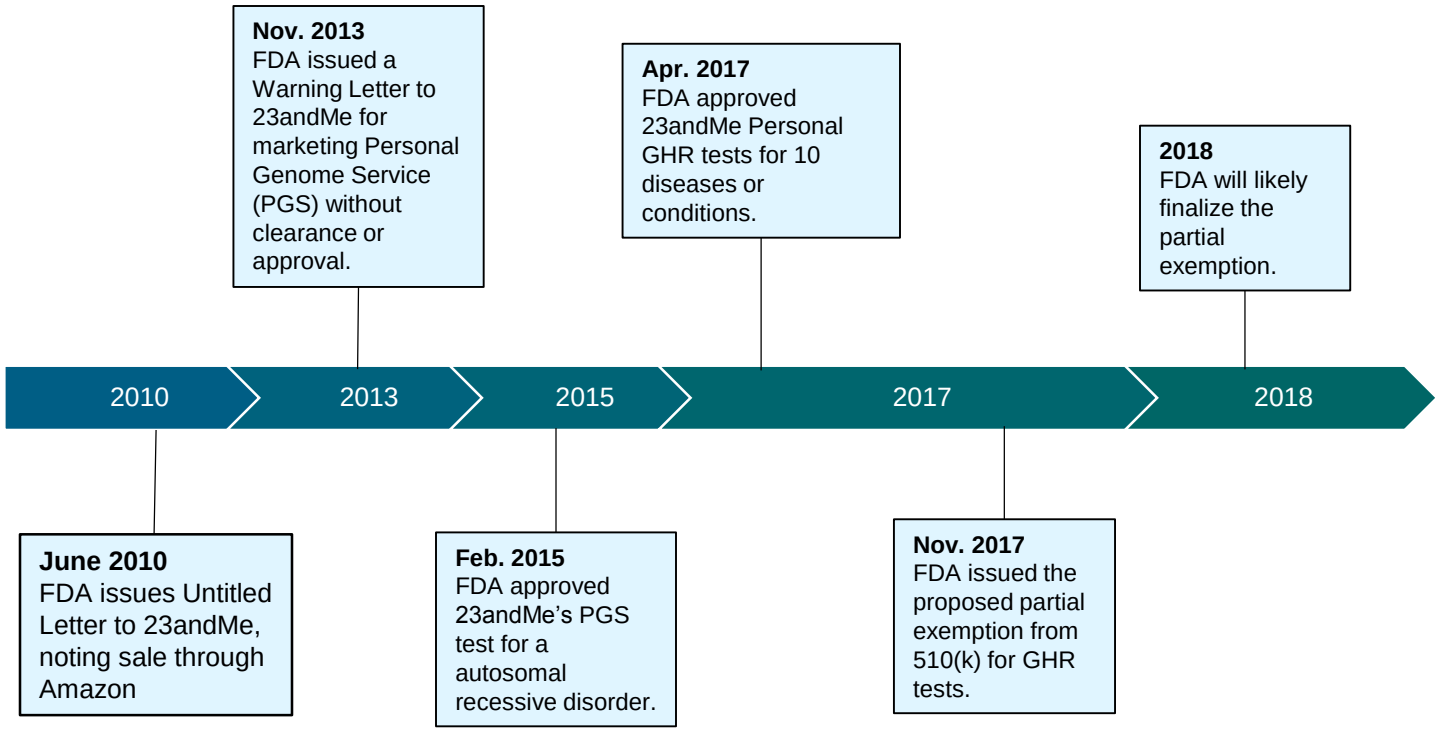
- On Jan. 13, 2017, FDA took an unusual move to publish a discussion paper. Issuing the discussion paper allows FDA to publicize, gauge and build support for its proposals on a controversial topic while avoiding the 60-day notice requirement from FDASIA.
- The discussion paper describes a risk-based approach that differs significantly from FDA's initial proposal in the 2014 draft guidance and reflects a "lighter touch" for most LDTs. Key provisions in FDA's proposal include:
  - **Prospective oversight** – The proposed framework focuses on new and significantly modified high and moderate-risk products and exempts "grandfathered" products from most FDA regulatory controls.
  - **Grandfathered products** – Products already on the market would not have to comply with FDA regulatory requirements, including premarket review, Quality System Regulation (QSR) or registration and listing requirements. "Grandfathered" products would, however, be subject to serious adverse event and malfunction reporting.
  - **Traditional, low-risk and other LDTs** – Certain new or significantly modified LDTs — including low-risk LDTs and LDTs for rare diseases — also would not be subject to regulatory requirements other than serious adverse event and malfunction reporting.
  - **Premarket evidence** – FDA would review clinical and analytical data in premarket submissions and expand its third-party premarket review program.
  - **LDT modifications** – FDA would have limited pre-market review of changes to cleared LDTs.
  - **Quality System requirements** – FDA would leverage CLIA certification requirements and only focus on three Quality System requirements: (1) design controls (21 C.F.R. § 820.30); (2) acceptance activities (21 C.F.R. § 820.80); and (3) procedures for corrective and preventive actions (CAPAs) (21 C.F.R. § 820.100).
  - **Conventional IVD kits** – The paper does not apply to conventional IVD kits, which would require premarket review.

Gottlieb Statements

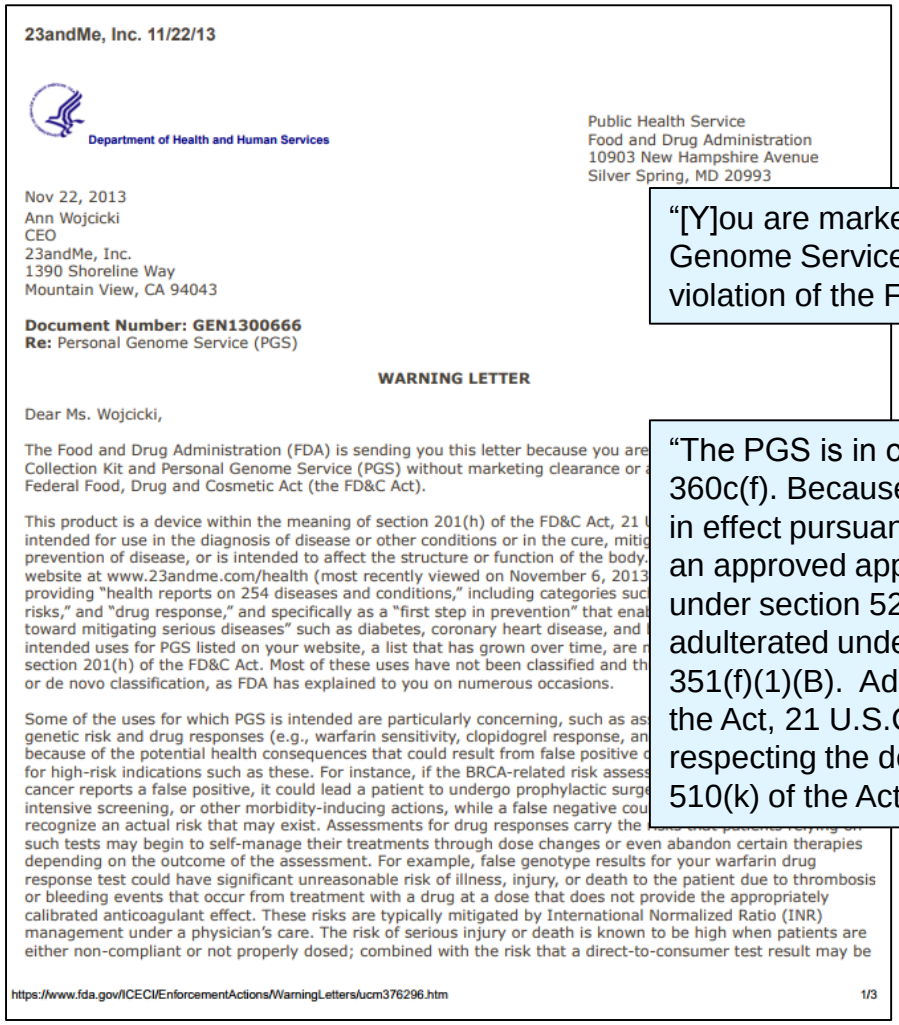
- During Friends of Cancer Research's "A Blueprint for Breakthrough" event on Sept. 13, 2017, FDA Commissioner Scott Gottlieb stated that Congress should legislatively lay out the government's role in overseeing LDTs and FDA will restrain itself before that.
  - "I think Congress needs to legislate. And I think that there are more opportunities here for Congress to think about doing something comprehensive. Because you've seen the stakeholders in this community start to align around some common principles in a way that they might not have been aligned certainly 10 years ago but even five years ago. So, **I think that the opportunity to see some comprehensive legislation that would address some of the real concerns that different parties have are there.**"
  - "Now that said, there's going to be incremental steps we take on a voluntary basis to provide more regulatory touch to certain aspects of these tests. **But I'm reluctant right now to do anything that would foreclose the opportunity for Congress to step in knowing that Congress has thought through this issue carefully, has done a lot of work on it already.** And I think from my standpoint, from a regulatory standpoint, the optimal solution is always to have a very clear legislative framework that you're working from rather than to try to do these things through guidance or other documents."
  - "[T]he economic case for using the diagnostics in conjunction with the therapeutics is just starting to evolve in a way that it's very, very compelling. It's always been compelling. But I think we're at an inflection point right now, and that's going to involve the broader diagnostic community -- and this is stepping outside my hat a little bit so I'll be very careful -- **to think differently about how these things are commercialized and whether or not it's a diagnostic being sold as a discrete entity and a drug being sold as a discrete entity, or are you selling a treatment system**[.]"
- Note that FDA does not exercise enforcement discretion for DTC tests regardless of whether they meet the definition of an LDT.

Direct-to-Consumer Genetic Health Tests

Recent History of DTC Genetic Test Regulation



2013 Warning Letters to 23andMe



23andMe, Inc. 11/22/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Nov 22, 2013
Ann Wojcicki
CEO
23andMe, Inc.
1390 Shoreline Way
Mountain View, CA 94043

Document Number: GEN1300666
Re: Personal Genome Service (PGS)

WARNING LETTER

Dear Ms. Wojcicki,

The Food and Drug Administration (FDA) is sending you this letter because you are
Collection Kit and Personal Genome Service (PGS) without marketing clearance or
Federal Food, Drug and Cosmetic Act (the FD&C Act).

This product is a device within the meaning of section 201(h) of the FD&C Act, 21
intended for use in the diagnosis of disease or other conditions or in the cure, mitig
prevention of disease, or is intended to affect the structure or function of the body.
website at www.23andme.com/health (most recently viewed on November 6, 2013
providing "health reports on 254 diseases and conditions," including categories suc
risks," and "drug response," and specifically as a "first step in prevention" that enab
toward mitigating serious diseases" such as diabetes, coronary heart disease, and
intended uses for PGS listed on your website, a list that has grown over time, are
section 201(h) of the FD&C Act. Most of these uses have not been classified and th
or de novo classification, as FDA has explained to you on numerous occasions.

Some of the uses for which PGS is intended are particularly concerning, such as as
genetic risk and drug responses (e.g., warfarin sensitivity, clopidogrel response, an
because of the potential health consequences that could result from false positive
for high-risk indications such as these. For instance, if the BRCA-related risk assess
cancer reports a false positive, it could lead a patient to undergo prophylactic surge
intensive screening, or other morbidity-inducing actions, while a false negative cou
recognize an actual risk that may exist. Assessments for drug responses carry the
such tests may begin to self-manage their treatments through dose changes or even abandon certain therapies
depending on the outcome of the assessment. For example, false genotype results for your warfarin drug
response test could have significant unreasonable risk of illness, injury, or death to the patient due to thrombosis
or bleeding events that occur from treatment with a drug at a dose that does not provide the appropriately
calibrated anticoagulant effect. These risks are typically mitigated by International Normalized Ratio (INR)
management under a physician's care. The risk of serious injury or death is known to be high when patients are
either non-compliant or not properly dosed; combined with the risk that a direct-to-consumer test result may be

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm376296.htm 1/3

"[Y]ou are marketing the 23andMe Saliva Collection Kit and Personal Genome Service (PGS) without marketing clearance or approval in violation of the Federal Food, Drug and Cosmetic Act (the FD&C Act)."

"The PGS is in class III under section 513(f) of the FD&C Act, 21 U.S.C. 360c(f). Because there is no approved application for premarket approval in effect pursuant to section 515(a) of the FD&C Act, 21 U.S.C. 360e(a), or an approved application for an investigational device exemption (IDE) under section 520(g) of the FD&C Act, 21 U.S.C. 360j(g), the PGS is adulterated under section 501(f)(1)(B) of the FD&C Act, 21 U.S.C. 351(f)(1)(B). Additionally, the PGS is misbranded under section 502(o) of the Act, 21 U.S.C. § 352(o), because notice or other information respecting the device was not provided to FDA as required by section 510(k) of the Act, 21 U.S.C. § 360(k)."

Approval of 23andMe PGS Test for Autosomal Recessive Disorder

- On Feb. 19, 2015, FDA authorized the marketing of 23andMe's Bloom Syndrome (a rare autosomal recessive disorder) carrier test, a DTC genetic test to determine whether a healthy person has a variant in a gene that could lead to their offspring inheriting the serious disorder.
- FDA also classified autosomal recessive carrier screening tests as class II:

  Autosomal recessive carrier screening gene mutation detection system is a qualitative in vitro molecular diagnostic system used for genotyping of clinically relevant variants in genomic DNA isolated from human specimens intended for prescription use or over-the-counter use. The device is intended for autosomal recessive disease carrier screening in adults of reproductive age. The device is not intended for copy number variation, cytogenetic, or biochemical testing. **21 C.F.R. § 866.5940.**

- In addition, FDA expressed its intention to exempt these devices from FDA premarket review, and finalized the exemption on Nov. 8, 2017.

> *"In general, carrier testing is a type of genetic testing performed on people who display no symptoms for a genetic disorder but may be at risk for passing it on to their children. A carrier for a genetic disorder has inherited one normal and one abnormal allele for a gene associated with the disorder. A child must inherit two abnormal alleles, one copy from each parent, in order for symptoms to appear."*
>
> — FDA Press Release

Approval of 23andMe Personal GHR Tests

- On Apr. 6, 2017, FDA approved marketing of 23andMe Personal GHR test, the first DTC tests authorized by FDA that provide information on an individual's genetic predisposition to certain medical diseases or conditions, which may help to make decisions about lifestyle choices or to inform discussions with a health care professional.

> *A genetic health risk assessment system is a qualitative in vitro molecular diagnostic system used for detecting variants in genomic DNA isolated from human specimens that will provide information to users about their genetic risk of developing a disease to inform lifestyle choices and/or conversations with a healthcare professional. This assessment system is for over-the-counter use. This device does not determine the person's overall risk of developing a disease.*

- The 23andMe GHR tests work by isolating DNA from a saliva sample, which is then tested for more than 500,000 genetic variants. The presence or absence of some of these variants is associated with an increased risk for developing any one of 10 diseases or conditions.

Proposed Partial Exemption from 510(k) for GHR Tests

- On Nov. 8, 2017, FDA published a notice, *Exemptions from Premarket Notification for Class II Devices*, proposing a simplified path to market for GHR tests under which, according to an FDA statement, manufacturers of these tests "would have to come to FDA for a one-time review to ensure that they meet the FDA's requirements, after which they may enter the market with new [genetic health risk] tests without further review." The notice also proposes to exempt four other class II devices from 510(k).
  - Partial exemption means developers of GHR tests would still have to submit a 510(k) before marketing a GHR test for the first time but could offer the test to detect additional variants or market new GHR tests without seeking FDA review.
- By allowing test developers to market tests for the detection of additional variants following initial FDA clearance, the proposed policy, if finalized, potentially reduces burden on GHR test developers in two ways:
  - First, premarket burden would be reduced because test developers would likely submit information concerning only their test's detection of a single or a small subset — as opposed to dozens or hundreds — of variants.
  - Second, test developers would be able to expand the indications of their marketed test without further FDA review.

What Is Not Included for the New Approach?

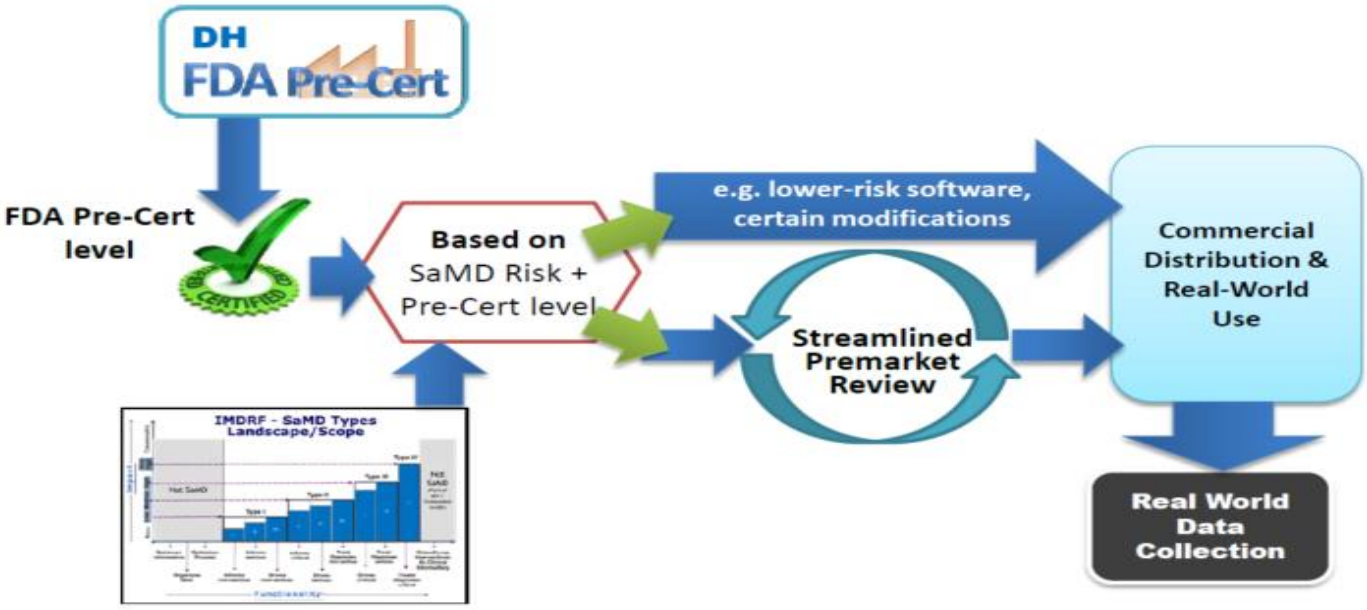
- The proposal to exempt GHR tests from 510(k) applies only to GHR tests "for which a misdiagnosis, as a result of using the device, would not be associated with high morbidity or mortality."
- Also, under 21 C.F.R. § 866.5950(b)(4), the tests could not be indicated for
  i. prenatal testing,
  ii. determining predisposition for cancer where the result of the test may lead to additional testing or treatment that may incur morbidity or mortality,
  iii. certain pharmacogenomics indications or
  iv. assessing the presence of deterministic autosomal dominant variants.
- Other special controls in 21 C.F.R. § 866.5950 include extensive requirements for labeling, public disclosure of information about test performance, use of FDA reviewed or exempt sample collection kits and requirements to establish analytical and clinical validity.
- In addition, the exemption from 510(k) remains subject to FDA's standard limitations on exemption, which describe certain changes to a 510(k) exempt device that trigger the need for a 510(k).

Open Questions

- Would a test that provides a risk profile for certain diseases based on the presence of multiple variants associated with disease risk fall within the relevant device classification regulation?
- For the precondition that “a misdiagnosis, as a result of using the device, would not be associated with high morbidity or mortality,” how — or whether — would this language apply to genetic health information that is not being marketed for diagnostic purposes?
  - If the language somehow applies, would this language track the exclusion from the GHR classification of certain indications for use or expands the exclusion, potentially excluding indications other than those associated with prenatal testing, cancer, pharmacogenomics and autosomal dominant variants?

Approach to Genetic Tests vs. Approach to Digital Health

- FDA's press statement compares the proposed policy for GHR tests to the precertification policy FDA is piloting for digital health products in that FDA is seeking a "firm-based" rather than product-based oversight model that focuses on the product developer's capabilities to consistently design and develop high-quality products.



Developments in Pharmacogenomics Tests

MSK-IMPACT De Novo Authorization

- On Nov. 15, 2017, FDA authorized Memorial Sloan Kettering Cancer Center's (MSK) IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets) tumor profiling test (assay), an in vitro diagnostic test that can identify a higher number of genetic mutations (biomarkers) that may be found in various cancers than any test previously reviewed by the agency.
- The IMPACT test uses next-generation sequencing (NGS) to rapidly identify the presence of mutations in 468 unique genes, as well as other molecular changes in the genomic makeup of a person's tumor.
- By identifying what genetic mutations are present in a particular tumor, the test results can provide patients and health care professionals with useful insight that may help inform how best to treat the cancer.

Approach to NGS Tests

- Along with the authorization, the FDA is also establishing a Class II regulatory pathway for the review of other NGS-based tumor profiling tests for use in patients diagnosed with cancer (21 C.F.R. § 866.6080).
- An NGS-based tumor profiling test is a qualitative in vitro diagnostic test intended to detect mutations in a broad panel of targeted genes that are somatically altered in malignant neoplasms from tumor specimens obtained from patients diagnosed with malignant solid neoplasms using targeted next-generation sequencing.
- Class II designation allows these types of tests to be eligible to use the FDA's 510(k) clearance process, either by submitting the application to the FDA directly or through an accredited third-party reviewer.

Changes Exempt from New 510(k)s

- MSK also provided FDA with protocols with specific procedures and acceptance criteria for modifications that could be anticipated at the time of submission. FDA cleared these as part of the authorization.
- Future modifications by MSK for the specified types of changes below that are made in accordance with the applicable validation strategy and the pre-specified success criteria would not require a new 510(k) submission. Significant changes such as adding new genes or variant types to the panel would require a new submission with appropriate validation.
  - New pre-analytical protocol, kits or reagents
  - New library preparation protocol, kits or reagents
  - Changes to probes for already analytically validated genes
  - New sequencing instrument or reagents using similar chemistry and technology, and the sequence depth and read length are not changed from previous platform
  - Update to underlying annotation database or transcript isoforms
  - Update to data management system and system database
  - Modification to an existing component of the analysis pipeline where the underlying algorithm or main parameter settings are not changed

Effect of State Approval

- FDA also announced the accreditation of the New York State Department of Health (NYSDOH) as an FDA third-party reviewer of in vitro diagnostics, including tests similar to the IMPACT test.
- Moving forward, laboratories whose NGS-based tumor profiling tests have been approved by NYSDOH do not need to submit a separate 510(k) application to the FDA. Instead, developers may choose to request that their NYSDOH application, as well as the state's review memorandum and recommendation be forwarded to the FDA for possible 510(k) clearance.
- Other accredited, third-party FDA reviewers also may become eligible to conduct such reviews and make clearance recommendations to the agency.
  - AABB
  - CENTER FOR MEASUREMENT STANDARDS OF INDUSTRIAL
  - NIOM - NORDIC INSTITUTE OF DENTAL MATERIALS
  - REGULATORY TECHNOLOGY SERVICES, LLC
  - THIRD PARTY REVIEW GROUP, LLC
  - TUV SUD AMERICA INC.

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