

Regulatory Landscape for Precision Medicine

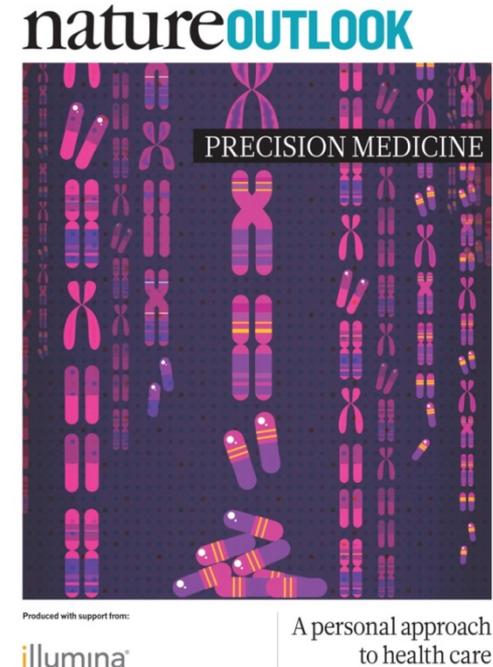
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*Office of In Vitro Diagnostics and Radiological Health,
FDA*

FOCR-Alexandria A Blueprint for Breakthrough Meeting
September 13, 2017

What is Precision Medicine Today?

- An approach to disease treatment and prevention that takes into account individual variability in lifestyle, environment, and genes
- A radical shift in how each of us can receive the best care possible based on our unique makeup
- Based on an old concept, but needing new insights, technologies, and science in order to advance



FDA Personalized Medicine Efforts

- Targeted Therapeutic Development
 - Pharmacogenetics
 - 192 drugs with pharmacogenetics in label (as of 7/29/17) across 18 therapeutic areas
 - Immunotherapies
- Personalized Biologics
 - 3D printed organs
 - Gene therapy
- Food Safety
 - Outbreak tracking
- Genetic Testing
 - Companion and Complementary Diagnostics
 - Liquid Biopsy
 - Next-Generation Sequencing (NGS)

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Companion Diagnostics

- The success of personalized medicine depends on having accurate, reproducible and clinically useful companion diagnostic tests to identify patients who can benefit from targeted therapies.
- Companion Diagnostics are those tests that provide information that is essential for the safe and effective use of a corresponding drug or biological product.

Many successful CoDx examples

Companion Diagnostics in Oncology	
40	Approved IVD Companion Diagnostic-Therapeutic Product Pairs
30	Approved IVD Companion Diagnostics
18	Approved Cancer Therapeutic Products
16	Molecular markers ALK, BRCA1, BRCA2, BRAF, C-KIT, EGFR, FLT3, HER-2/NEU, IDH2, KIT, KRAS, NRAS, PDGFRB, PD-L1, ROS1, 17p deletion

- www.fda.gov/companiondiagnostics

(#'s as of 09/11/2017)

<p>FoundationFocus™ CDxBRCA</p> <p>1st NGS CDx</p>	<p>Next generation sequencing based in vitro diagnostic device for qualitative detection of BRCA1 and BRCA2 alterations in formalin-fixed paraffin-embedded (FFPE) ovarian tumor tissue. Results of the assay are used as an aid in identifying ovarian cancer patients for whom treatment with Rubraca™ (rucaparib) is being considered.</p>
<p>Oncomine™ Dx Target Test</p> <p>1st CDx for multiple indications</p>	<p>Qualitative in vitro diagnostic test that uses targeted high throughput, parallel-sequencing technology to detect single nucleotide variants (SNVs) and deletions in 23 genes from DNA and fusions in ROS1 from RNA isolated from formalin- fixed, paraffin-embedded (FFPE) tumor tissue samples from patients with non-small cell lung cancer (NSCLC) using the Ion PGM™ Dx System. Aid in selecting NSCLC patients for treatment with Tafenlar, Iressa, and Xalkori.</p>
<p>Praxis™ Extended RAS Panel</p> <p>1st CDx based on negative mutation status</p>	<p>Qualitative in vitro diagnostic test using targeted high throughput parallel sequencing for the detection of 56 specific mutations in RAS genes [KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4)] in DNA extracted from formalin-fixed, paraffin-embedded (FFPE) colorectal cancer (CRC) tissue samples. Aid in the identification of patients with colorectal cancer for treatment with Vectibix® (panitumumab) based on a no mutation detected test result.</p>

Emerging Paradigm – Complementary Diagnostics

- A **companion diagnostic** is an IVD that provides information that is essential for the safe and effective use of a corresponding therapeutic product
- A **complementary diagnostic** is an IVD that identifies a biomarker-defined subset of patients with a different benefit-risk profile than the broader population for which a therapeutic product is indicated, but that is not a prerequisite for receiving the therapeutic product

“Complementary” IVD Approval Examples

	Intended Use (excerpts)
PD-L1 IHC 28-8 pharmDx	PD-L1 expression as detected by PD-L1 IHC 28-8 pharmDx in non-squamous NSCLC may be associated with enhanced survival from OPDIVO® (nivolumab).
PD-L1 IHC 28-8 pharmDx	Positive PD-L1 status as determined by PD-L1 IHC 28-8 pharmDx in melanoma is correlated with the magnitude of the treatment effect on progression-free survival from OPDIVO®.
Ventana PD-L1(SP142) CDX ASSAY	PD-L1 expression in $\geq 5\%$ IC determined by VENTANA PD-L1 (SP142) Assay in urothelial carcinoma tissue is associated with increased objective response rate (ORR) in a non-randomized study of TECENTRIQ™ (atezolizumab).

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FDA Approval of a Liquid Biopsy Test

cobas EGFR Mutation Test v2 (using plasma specimens)

Roche Molecular Systems, Inc.

- **First “liquid biopsy test” approved for NSCLC**
- Approved on June 1, 2016, as a companion diagnostic to identify patients eligible for treatment with Tarceva (erlotinib).
- Approved on September 28, 2016, as a companion diagnostic to identify patients eligible for treatment with Tagrisso (osimertinib).
- Test was previously approved for same indication using FFPE tissue specimens.

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In Vitro Diagnostics in the Age of Precision Medicine

Traditional testing



Next
generation



Regulatory Issues

- NGS tests can have broad intended uses
 - Can't predefine the results that will be obtained
 - Often don't know the disease that will be diagnosed until the test is performed
- Validation of NGS tests at each variant is not feasible
- Conventional requirements for review
 - Review each claim
 - Review modifications that affect the safety and effectiveness of a test

Developing a Nimble Regulatory Approach for Genomic Tests



THE PRECISION MEDICINE INITIATIVE

To enable a new era of medicine through research and technology that empowers patients, researchers, and providers to work together toward development of individualized treatments.

Vision: Implement new regulatory policies to promote research and accelerate the translation of precision medicine technologies into treatments that *benefit patients*.

NGS draft guidances (July 2016)

- Describe a regulatory pathway for NGS-based tests for certain uses
- Analytical standards draft guidance - <https://www.regulations.gov/docket?D=FDA-2016-D-1270>
- Databases draft guidance - <https://www.regulations.gov/docket?D=FDA-2016-D-1233>
- Anticipate and support the needs of rapidly-evolving NGS technologies
- Intended to ensure **patient safety**, encourage **innovation**, and assure the **quality and reliability** of NGS-based tests and promote adoption of NGS-based tests into clinical practice
- NGS tests developed according to these guidances would have an **efficient path to market**

Use of Standards in FDA Regulatory Oversight of NGS-Based IVDs for Diagnosing Germline Diseases



- The draft guidance presents recommendations for the **design, development, and validation** of NGS-based tests to aid in diagnosis of genetic diseases or conditions:
 - Describes approach to test **design** (accommodates different test designs, indications for use, user needs, components, methods)
 - Test **performance characteristics** (including accuracy, precision)
 - Test **run quality** metrics (including read depth, completeness, performance thresholds)
 - Additional recommendations
- May form the basis for future **FDA-recognized standard(s)** and/or special controls.

Scope:

The draft guidance applies only to targeted or Whole Exome Sequencing NGS-based tests intended to aid in the diagnosis of individuals with suspected germline diseases or other (germline) conditions

Evidence

- Conventional regulatory approach requires submission of valid scientific evidence to support the claimed intended use of IVDs in marketing submissions to FDA



Benefits of Using Genetic Databases

- Evidence generated by multiple parties; **aggregated data** provide a **stronger evidence** base (i.e., current state of scientific knowledge)
- As clinical **evidence improves**, new assertions could be supported
- Draft guidance applies to **publicly** accessible databases only
- Recommendations for administrators of databases to demonstrate that the database can be considered a source of “**valid scientific evidence**”
- **Voluntary** database recognition pathway (similar to standards recognition)
- Evidence from databases **could support the clinical validity** of NGS-based tests

Draft Guidance - Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics

<https://www.federalregister.gov/articles/2016/07/08/2016-16200/use-of-public-human-genetic-variant-databases-to-support-clinical-validity-for-next-generation>

FDA's Concepts for NGS Regulation

- **Technical/analytical standards for NGS**
 - Test developers that meet these standards may not have to submit an application to FDA.
 - Standards would be developed with the scientific community, and can be updated as science and technology advance.
- **Use of curated databases to provide clinical evidence**
 - Use “regulatory grade” databases as information sources to support the link between genetic variation and health/disease.
 - Test developers may be able to use such databases in lieu of traditional clinical studies.

FDA - Creating an environment that enables innovation and regulatory efficiency while protecting patients and public health



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Current State of Precision Medicine Development

September 13, 2017

Julie Dixon, PhD

Group Director, Global Regulatory
Sciences Bristol-Myers Squibb

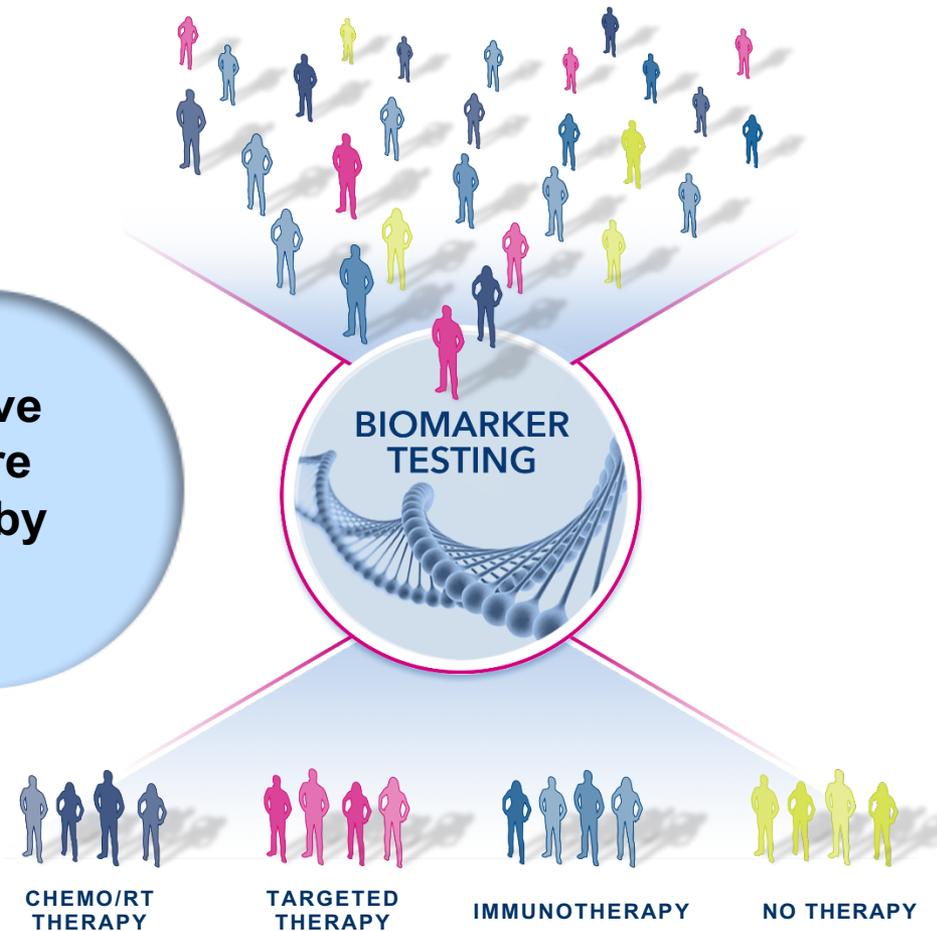
Key Areas for Discussion

- **Potential areas where key stakeholders can work together to aid in the development and application of NGS diagnostic platforms**

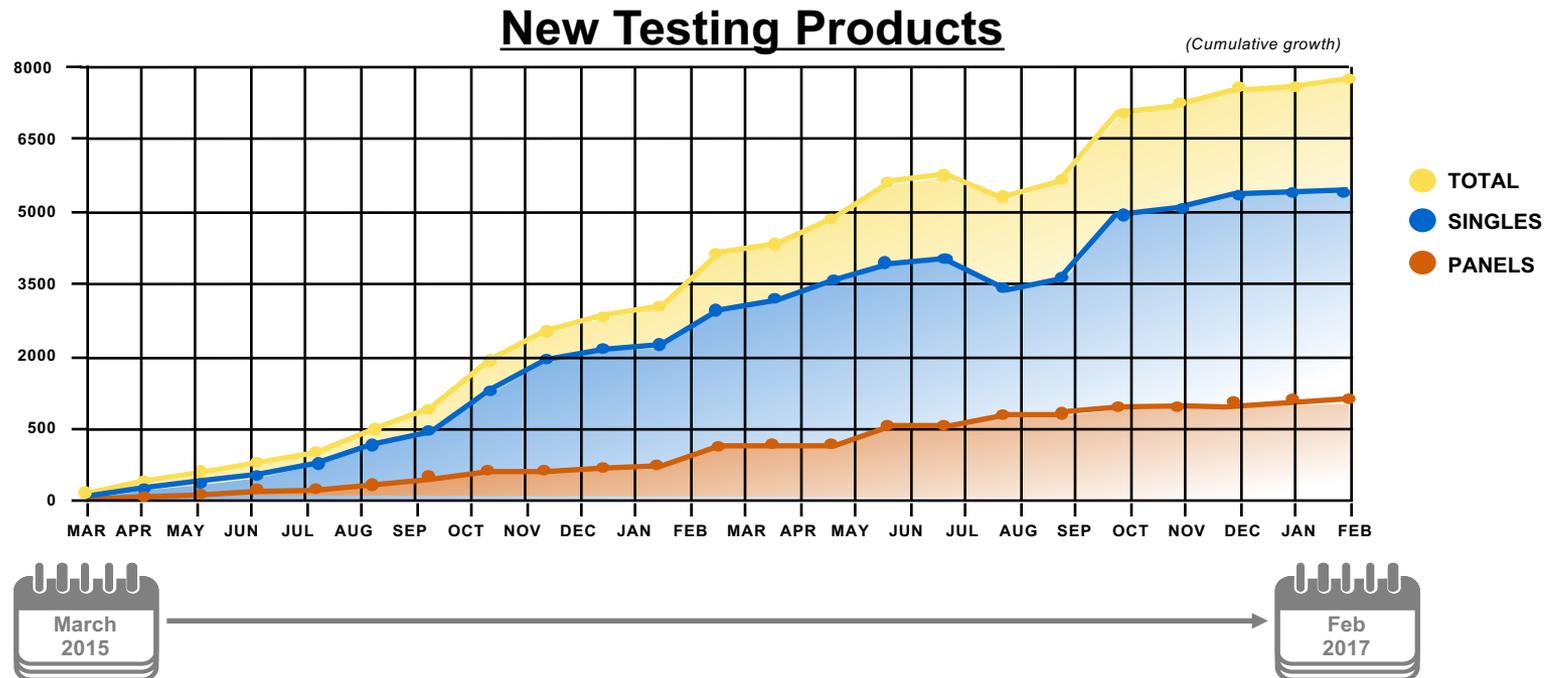
- **Standardization, accessibility, and reliability of NGS platforms in clinical settings to further drive innovation in personalized medicine**

Science and Technology Are Driving Innovation in Cancer Therapy

Advances in technology have enabled a shift towards more precise treatments defined by tumor biology



Use of Genetic Testing Has Exponentially Increased in Recent Years



69,104*

Genetic testing products

On average, 10 new products enter the market every day

almost
8,000*

New testing products

155

Pharmacogenomic biomarkers are included on FDA-approved drug labels

Adapted from personalizedmedicinecoalition.org and NextGxDx.

*As of March 1, 2017. A testing product is defined as an orderable unit from a US-based, CLIA-certified laboratory.

Recent FDA Approvals for NGS-Based Diagnostics in Oncology

NGS has enabled a shift from assessment of a single biomarker linked to a single drug to multiple biomarkers linked to multiple drugs

	Manufacturer	Test	Target	Tumor Type/Drug	Intended Use
1 marker–1 drug	Roche ^{1,2}	cobas® EGFR Mutation Test v2	<i>EGFR</i>	<ul style="list-style-type: none"> NSCLC: Osimertinib or Erlotinib 	<ul style="list-style-type: none"> Companion diagnostic
Multiple markers–1 drug	Foundation Medicine ³	FoundationFocus CDxBRCA Assay	<i>BRCA1, BRCA2</i>	<ul style="list-style-type: none"> Ovarian: Rucaparib 	<ul style="list-style-type: none"> Companion diagnostic
	Illumina ⁴	Praxis Extended RAS Panel	56 mutations in <i>KRAS</i> and <i>NRAS</i>	<ul style="list-style-type: none"> Colorectal cancer: Panitumumab 	<ul style="list-style-type: none"> Companion diagnostic
Multiple markers –multiple drugs	ThermoFisher Scientific ⁵	Oncomine Dx Target Test	23 genes	<ul style="list-style-type: none"> NSCLC: Multiple drugs (multiple companies) 	<ul style="list-style-type: none"> Companion diagnostic Analytical performance only

Foundation Medicine Receives FDA Approval of FoundationFocus™ CDxBRCA as a Companion Diagnostic for Rubraca™ (rucaparib) for the Treatment of Women with Ovarian Cancer

Illumina Announces FDA-approved Next-Generation Sequencing Cancer Companion Diagnostic Test Kit

FDA Approves First Companion Diagnostic Test to Simultaneously Screen for Multiple Non-Small Cell Lung Cancer Therapies

NGS May Enable Tumor-Agnostic Drug Development

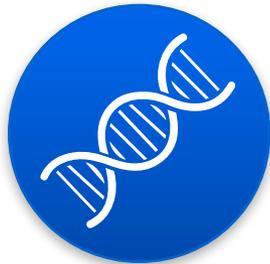


- A comprehensive account of tumor mutations evaluated by NGS may lead to tumor-agnostic development

FDA approves first cancer treatment for any solid tumor with a specific genetic feature
- FDA press release

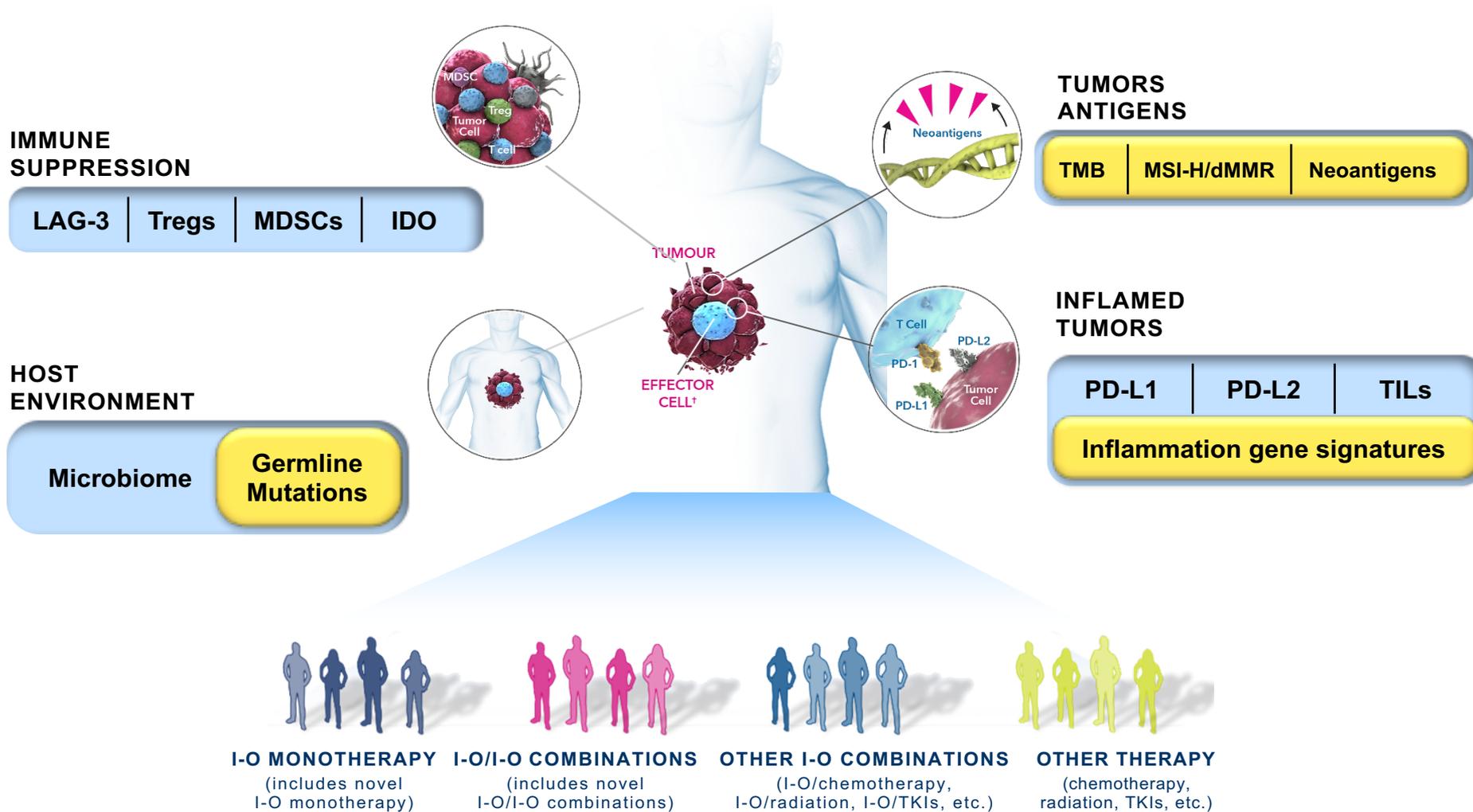
May 23, 2017

- Tumor-agnostic approval for Keytruda in MSI-High/dMMR tumors signifies a paradigm shift in cancer treatment and regulatory landscape



- TMB, an emerging biomarker analyzed by NGS, may evolve as a tumor-agnostic biomarker for I-O therapy

NGS Has the Potential to Select Patients for Precision I-O Therapy



NGS can be used to identify ideal therapies for patients

Drivers and Barriers for Incorporating NGS-Based Diagnostics in Clinical Trials



Drivers



- Increased speed of development
- Enhanced probability of technical success
- Improvement in magnitude of treatment effect
- Identification of multiple actionable markers simultaneously

Barriers



- Appropriate level of analytical validation and standardization
- Multiple tests with different performance characteristics
- Data access and informatics to establish clinical relevance
- Informed consent and sample collection

Drivers and Barriers for Incorporating NGS-Based Diagnostics in Medical Practice



Drivers



- Improved patient outcomes through precision medicine
- Maximize information for therapeutic decision making
- Minimize sample and number of diagnostic tests needed

Barriers



- Test availability, cost and reimbursement
- Turnaround time
- Tissue requirements
- Lack of standardized result reporting

Collaboration Will be Required to Address NGS Standardization to Realize Its Full Potential

Topics for today

How can we establish analytical standards and identify critical performance characteristics?

What modifications should be made to streamline the approval of diagnostic tests?

Which steps will best drive uptake of high quality precision medicine tools?

Topics for the future

Establishing sample pre-analytical standardization

Steps to create consistent guidelines for lab reports and interpretation

Establishing uniform standards based on clinically driven evidence

Who Sets the Standard?

Thank You