Data in Cancer Genomics

Thomas Wieland
05 September 2024

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Contents

Introduction

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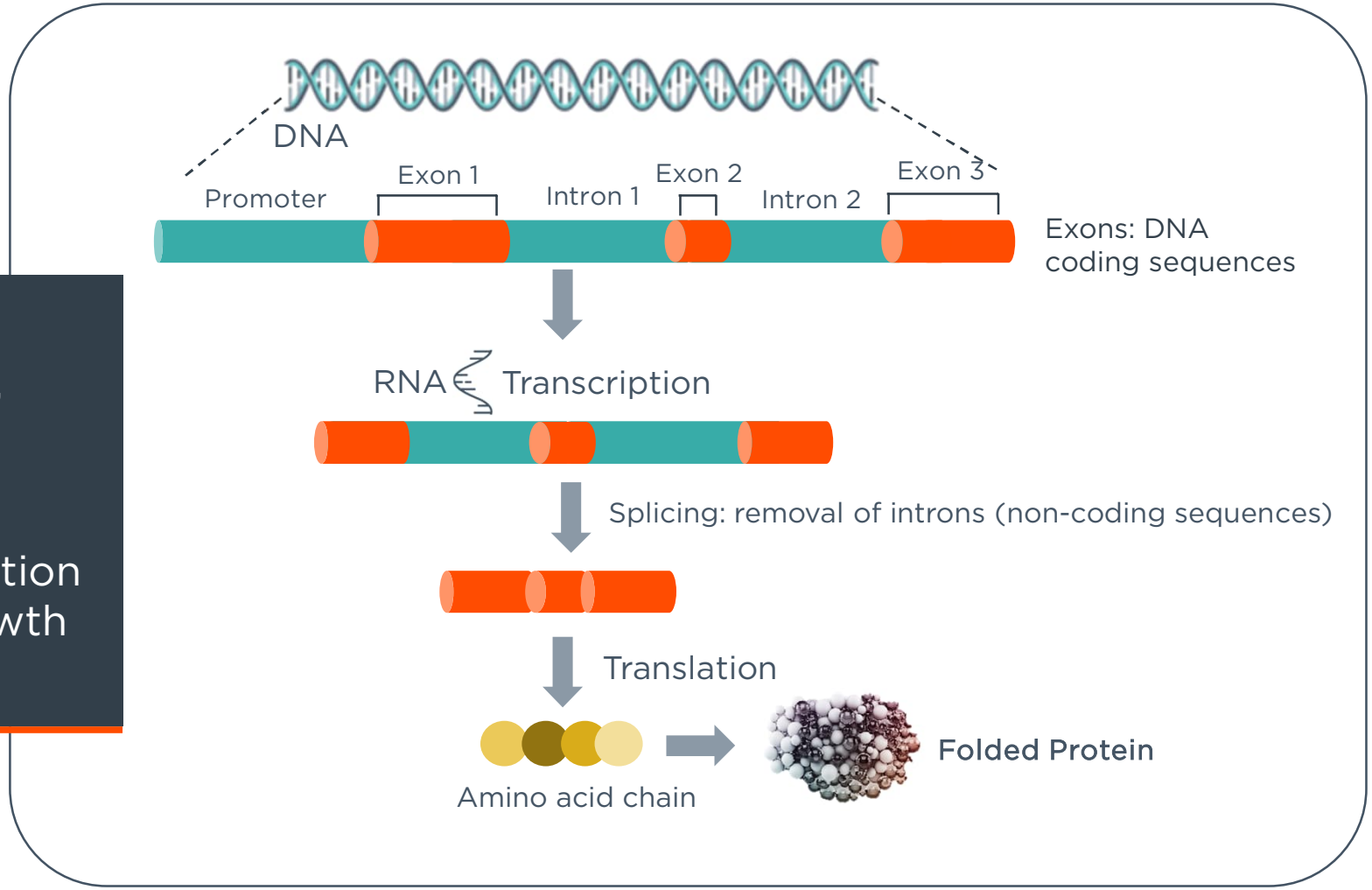
The Roles of Genes in Normal Cells

DNA provides instructions for transcription and RNA production, which directs translation/protein synthesis[1]

Protein folding is required for function in cellular processes including growth and death[1]



1. Kolch W. *Nature Reviews Cancer.* 2015;15:515-527.

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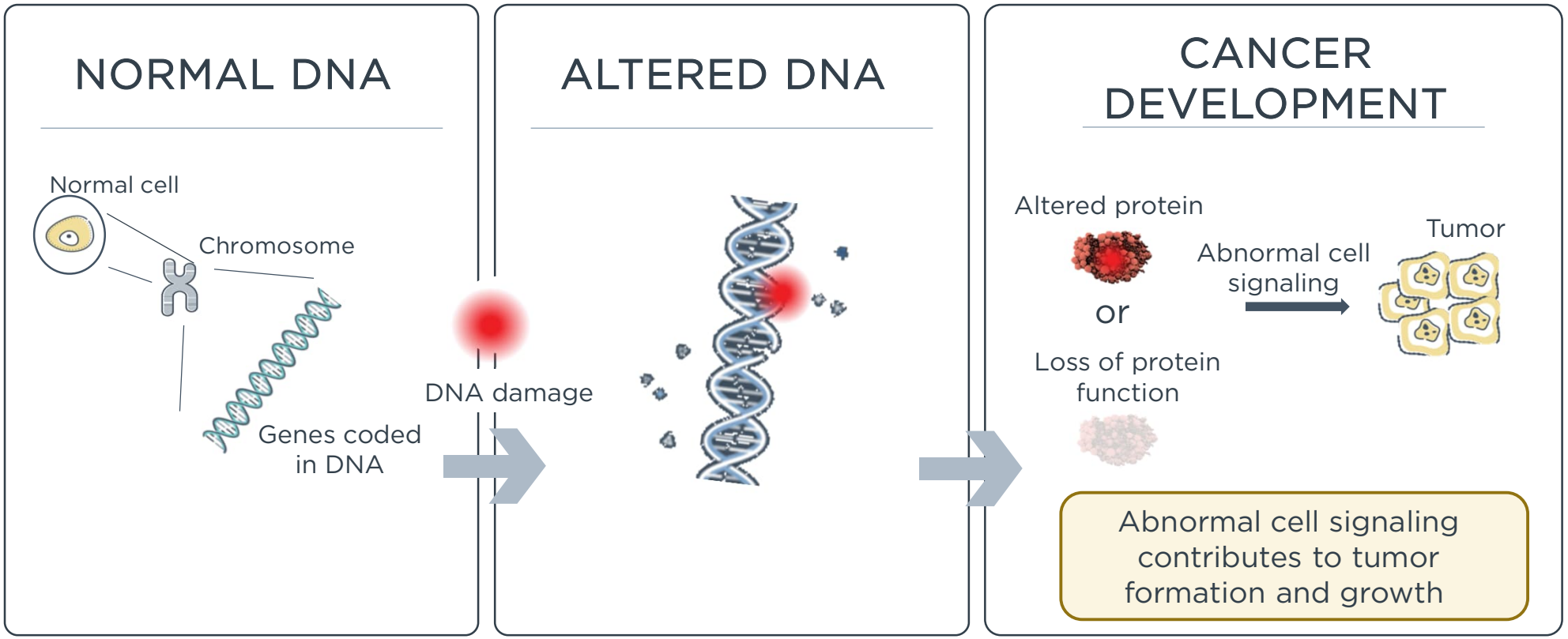
Studying Genomic Alterations in Cancer

Multiple factors can introduce DNA alterations that may impact protein function and contribute to tumor formation[1,2]



1. Kolch W. *Nature Reviews Cancer*. 2015;15:515-527. 2. Roos WP. *Nature Reviews Cancer*. 2016;16:20-33.

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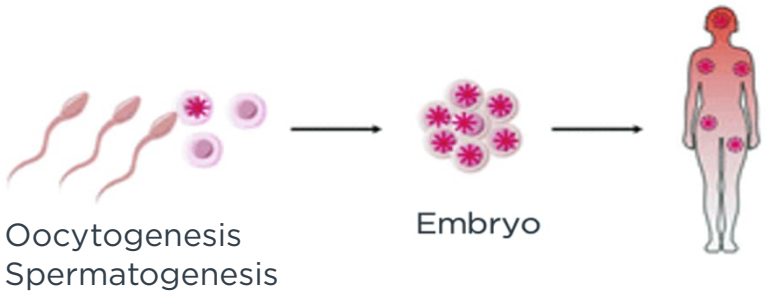
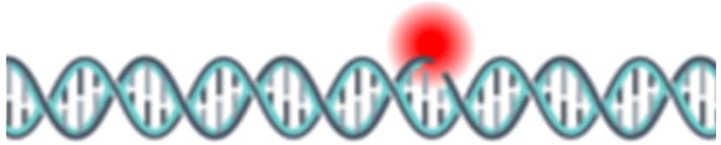
Gene Alterations Can Be Germline or Somatic

GERMLINE



- Some people have inherited mutations that increase their risk of cancer[1]
- Germline mutations occur in every cell in the body
- Examples: *BRCA1* and *BRCA2*[2]

SOMATIC



DNA breaks caused by:
Cancer-causing agents | Radiation
Mistakes in DNA copying | Viral infections

- DNA is exposed to damage every day; this may cause non-inherited gene mutations to occur[1]
- Exposure to risk factors increases the chances of gene mutations[1]
- Mutation rate is almost 100 times higher than the germline mutation rate

1. Vijg J. *Cell.* 2020;182(1):12-23; 2. Jiang M. *Acta Pharm Sin B.* Oct 2021;11(10):2983-2994.
Image adapted from https://www.ks.uiuc.edu/Research/dbps/dbp7.html. Accessed February 2, 2024.

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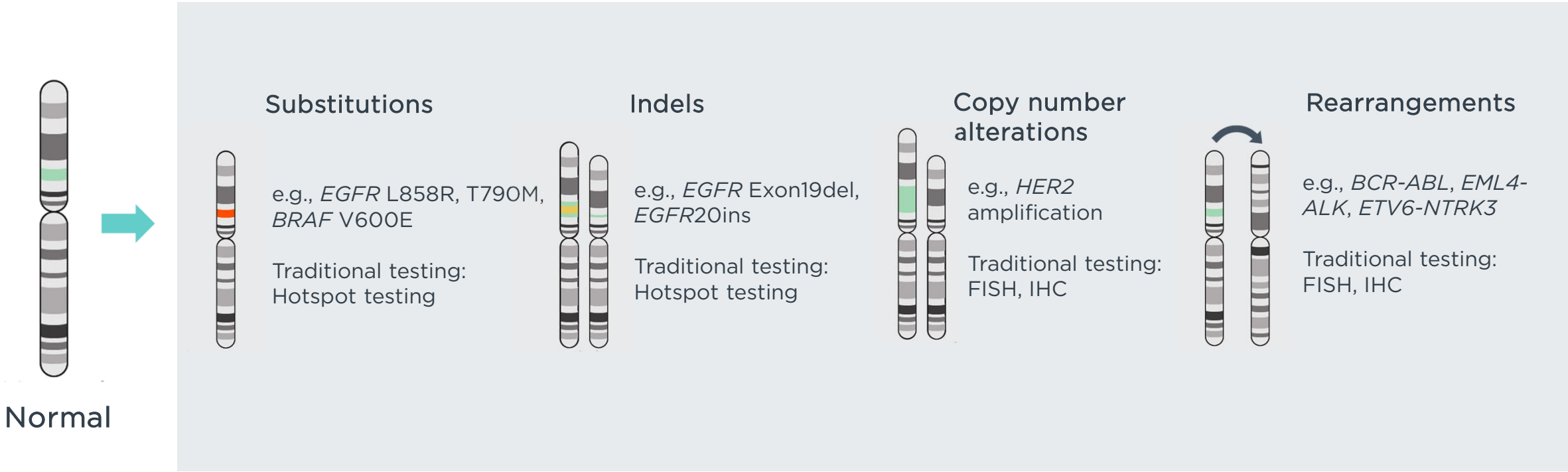
DNA Alterations Contribute to Cancer Initiation and Progression

4 types of DNA alterations that are detected by CGP



Identification of actionable genetic alterations has led to development of molecularly targeted therapies in cancer

CGP = comprehensive genomic profiling, FISH = fluorescence in-situ hybridization, IHC = immunohistochemistry, indels = insertions/deletions

Halliday PR. *Curr Oncol Rep*. 2019;21(3):21; Ross JS. *Cancer*. 2018;124(7):1358-1373; Stransky N. *Nat Commun*. 2014;5:4846.

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Molecular Testing and Comprehensive Genomic Profiling Overview

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Molecular Testing Is Recommended by Professional Guidelines for a Growing Number of Cancer Types

SOLID TUMORS

- Breast Cancer[1]
- Non-Small Cell Lung Cancer*[3]
- Cutaneous Melanoma[6]
- Thyroid Cancer[8]
- Hepatobiliary Cancers[10]
- Central Nervous System Cancers[12]
- Esophageal & Esophagogastric Junction[14]
- Gastrointestinal Stromal Tumors[16]
- Prostate Cancer[2]
- Colon Cancer[4] and Rectal Cancer[5]
- Bladder Cancer[7]
- Endometrial Cancer[9]
- Pancreatic Cancer[11]
- Gastric Cancer[13]
- Ovarian Cancer[15]
- Bone Cancer[17]

HEMATOLOGIC MALIGNANCIES

- Chronic Myeloid Leukemia[18]
- Acute Myeloid Leukemia[19]
- Acute Lymphocytic Leukemia[20]
- Myelodysplastic Syndromes[21]
- Myeloproliferative Neoplasms[22]

*The NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for NSCLC provide recommendations for individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays or commercial laboratories. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

[1–22]For details of NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) References, please see the reference slides.

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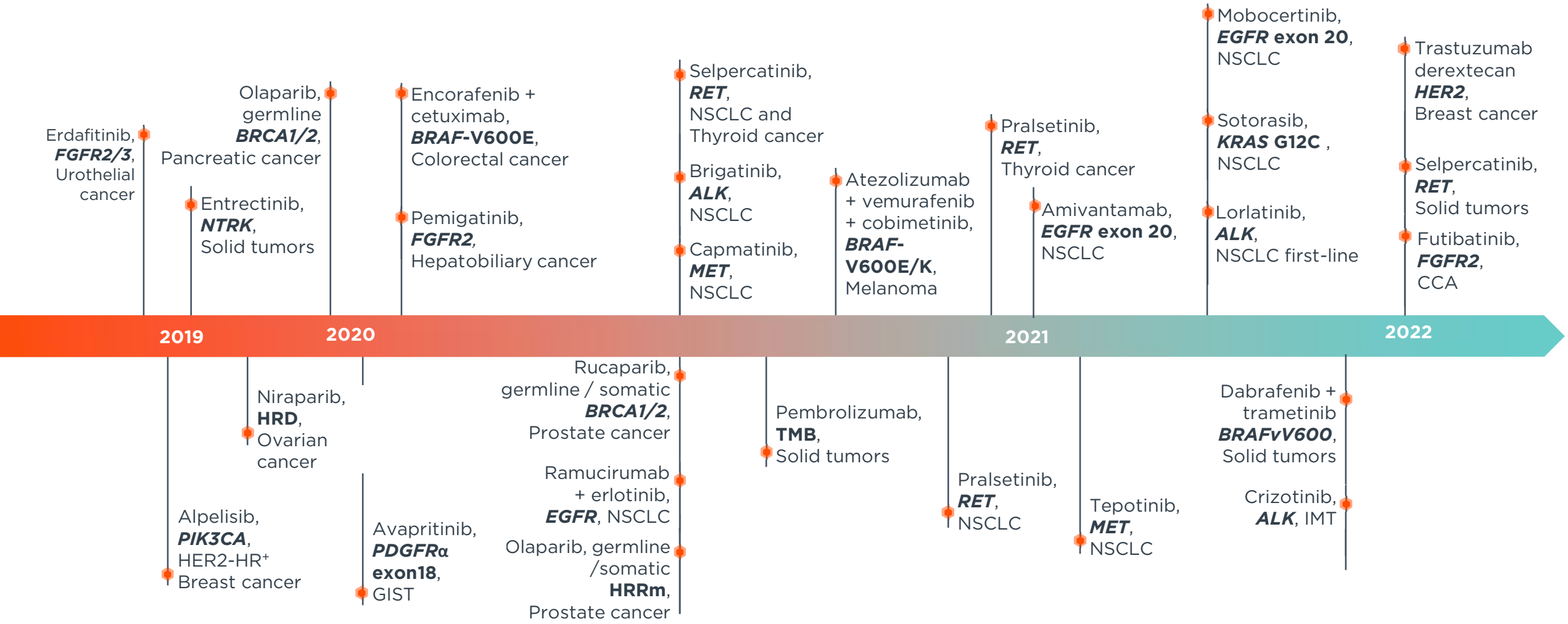
Wave of Recent Targeted Therapy Approvals



1. Mateo J. *Nat Med*. 2022;28(4):658-665.

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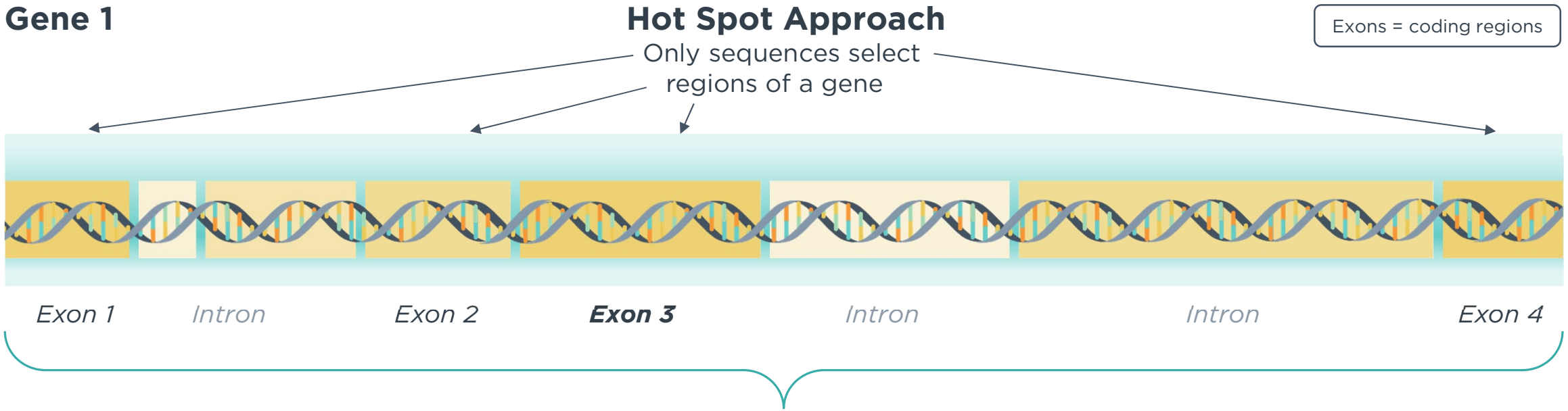
Comprehensive Genomic Profiling (CGP) Interrogates Entire Coding Sequences of Cancer-Relevant Genes



Comprehensive Genomic Profiling: Sequences Entire Coding Regions of Genes

Can identify:

- **ALL** base substitutions
- **ALL** insertions/deletions
- **ALL** copy number alterations
- **Select** rearrangements within those genes

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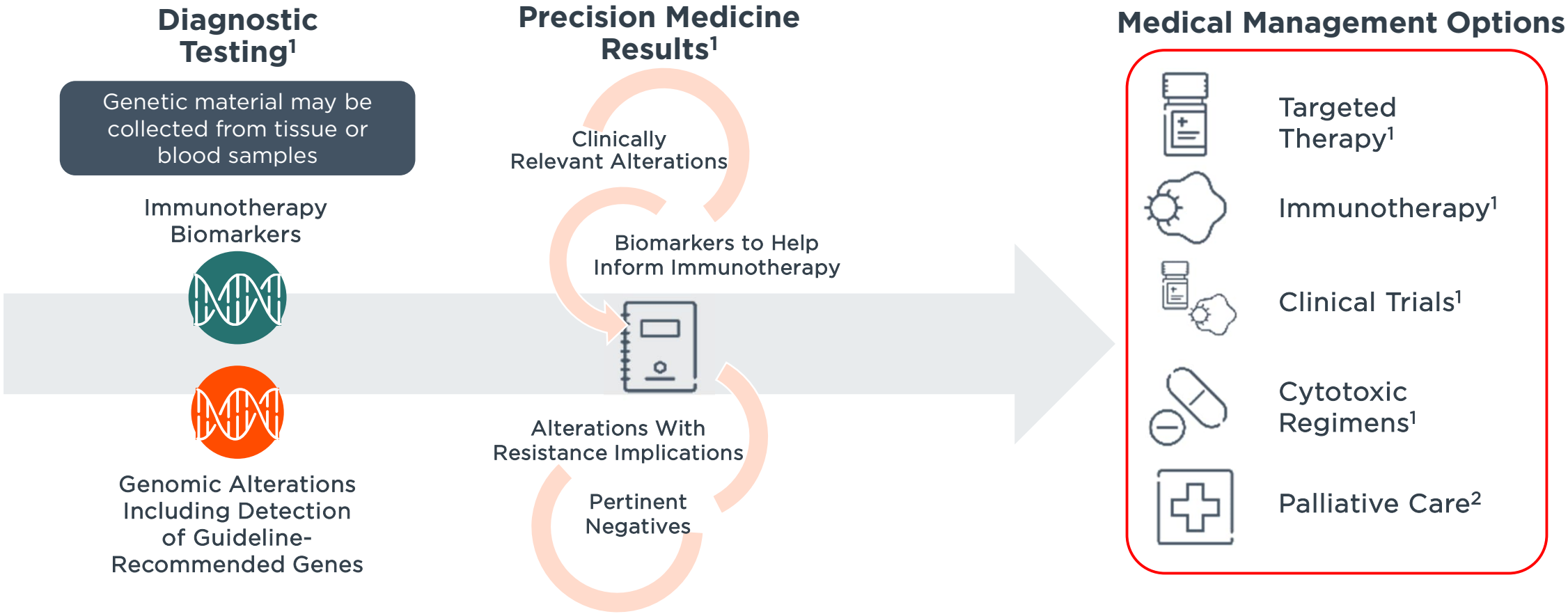
Comprehensive Genomic Profiling (CGP) Can Help Identify the Right Treatment Approach



1. National Cancer Institute. Biomarker Testing for Cancer Treatment. Updated December 14, 2021. Accessed February 2, 2024. https://www.cancer.gov/about-cancer/treatment/types/biomarker-testing-cancer-treatment; 2. National Cancer Institute. Palliative Care in Cancer. Reviewed November 1, 2021. Accessed February 2, 2024. https://www.cancer.gov/about-cancer/advanced-cancer/care-choices/palliative-care-fact-sheet.

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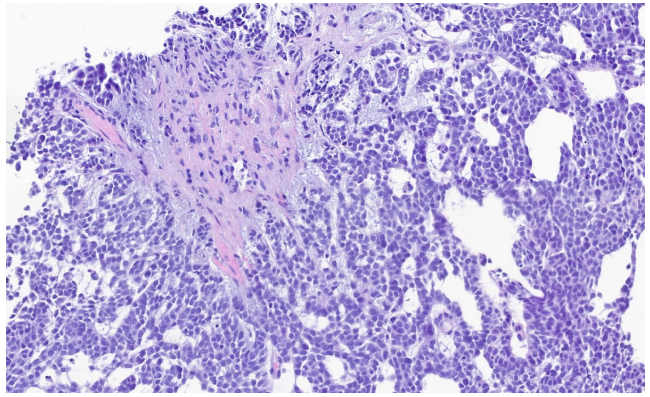
CGP May Clarify Diagnosis and Inform Therapy Options

Patient with tumor diagnosed as metastatic small-cell carcinoma



CGP reveals an elevated TMB and inactivation of *PTCH1*

Biomarker Findings

Tumor Mutational Burden - 50 Muts/Mb
Microsatellite status - MS-Stable

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

PTCH1 **L448fs*8**
TP53 **R248W, P278L**

† See About the Test in appendix for details.

CGP results in updated diagnosis of metastatic basal cell carcinoma

PATHOLOGIST COMMENTS

Douglas A. Mata, MD, MPH 20-Jan-2022

The test requisition form diagnosis of metastatic carcinoma with neuroendocrine differentiation involving a supraclavicular lymph node is noted. Review of the next-generation sequencing data reveals an elevated tumor mutational burden with an abundance of G>A,C>T and CC>TT,GG>AA transitions consistent with UV radiation-mediated mutagenesis, biallelic inactivation of TP53, and inactivation of the sonic hedgehog receptor PTCH1. Taken together, the findings are most consistent with metastatic cutaneous basal cell carcinoma with neuroendocrine differentiation. This case has therefore been curated with a disease ontology (DO) of "skin basal cell carcinoma" in order to highlight relevant therapies in association with the PTCH1 variant on the professional services page. Clinicopathologic correlation is advised.

CGP = comprehensive genomic profiling, TMB = Tumor Mutational Burden

1. Mata, DA. *JAMA NOW*. 2022;5(3): e223833. doi:10.1001/jamanetworkopen.2022.3833.

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Key Takeaways – CGP Overview

Molecular testing is **recommended by professional guidelines** and may detect actionable genetic alterations with targeted therapy options

Comprehensive genomic profiling (CGP) identifies all 4 types of genomic alterations associated with cancer

CGP may clarify diagnosis and treatment options

Foundation Medicine's CGP approach uses hybrid capture-based NGS to identify genomic alterations

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NGS = next-generation sequencing

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CGP at Foundation Medicine

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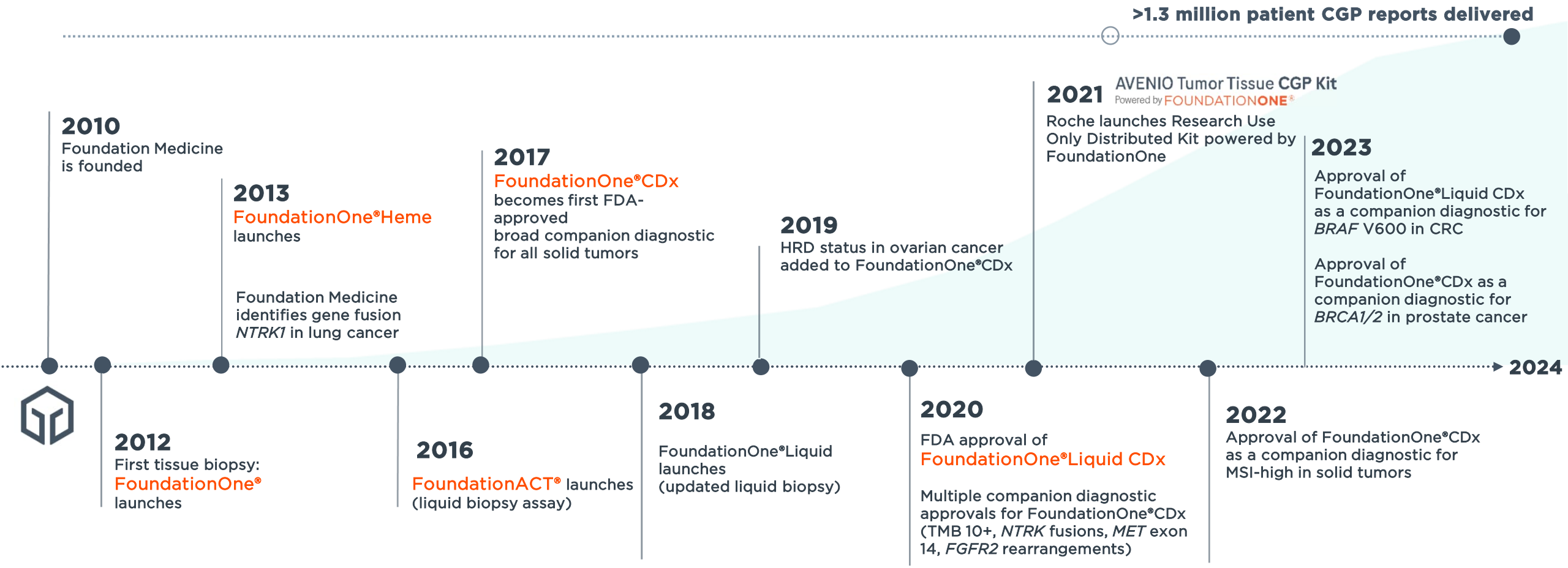
Pioneering Advances for Precision Cancer Care



CGP = comprehensive genomic profiling, CRC = colorectal cancer, HRD = homologous recombination deficiency, MSI = microsatellite instability

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Workflow of Foundation Medicine CGP With NGS

Multiple teams involved in the process

Physician
submits order

Pathology
reviews histology and assigns tumor type

Lab
extracts and sequences DNA and/or RNA

Computational Pipeline

Clinical Bioinformatics
reviews variants and quality metrics

Report Transmittal
sends out report

Pathology
reviews and approves

Translational Oncology & Clinical Reporting

- Create personalized clinical genomic readout
- Functional evaluation of variants
- Create interpretive content
- Assess therapies for sensitivity and resistance
- Match applicable clinical trials

CGP = comprehensive genomic profiling, NGS = next-generation sequencing.

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MG35
TW1

The Most Experience with Comprehensive Genomic Profiling in the Industry[1]

1,300,000+
PATIENT CGP REPORTS DELIVERED

800+
PEER-REVIEWED PUBLICATIONS

~200
PEOPLE IN DRY LAB R&D AND OPS

THE MOST FDA-APPROVED

COMPANION DIAGNOSTIC CLAIMS ON THE MARKET

FOUNDATIONONE® CDx

35+
COMPANION DIAGNOSTIC CLAIMS

5
GROUP CLAIMS

FOUNDATIONONE® LIQUID CDx

10+
COMPANION DIAGNOSTIC CLAIMS

1
GROUP CLAIM

1. Data on file. Foundation Medicine, Inc, 2022

US-PF-2300019

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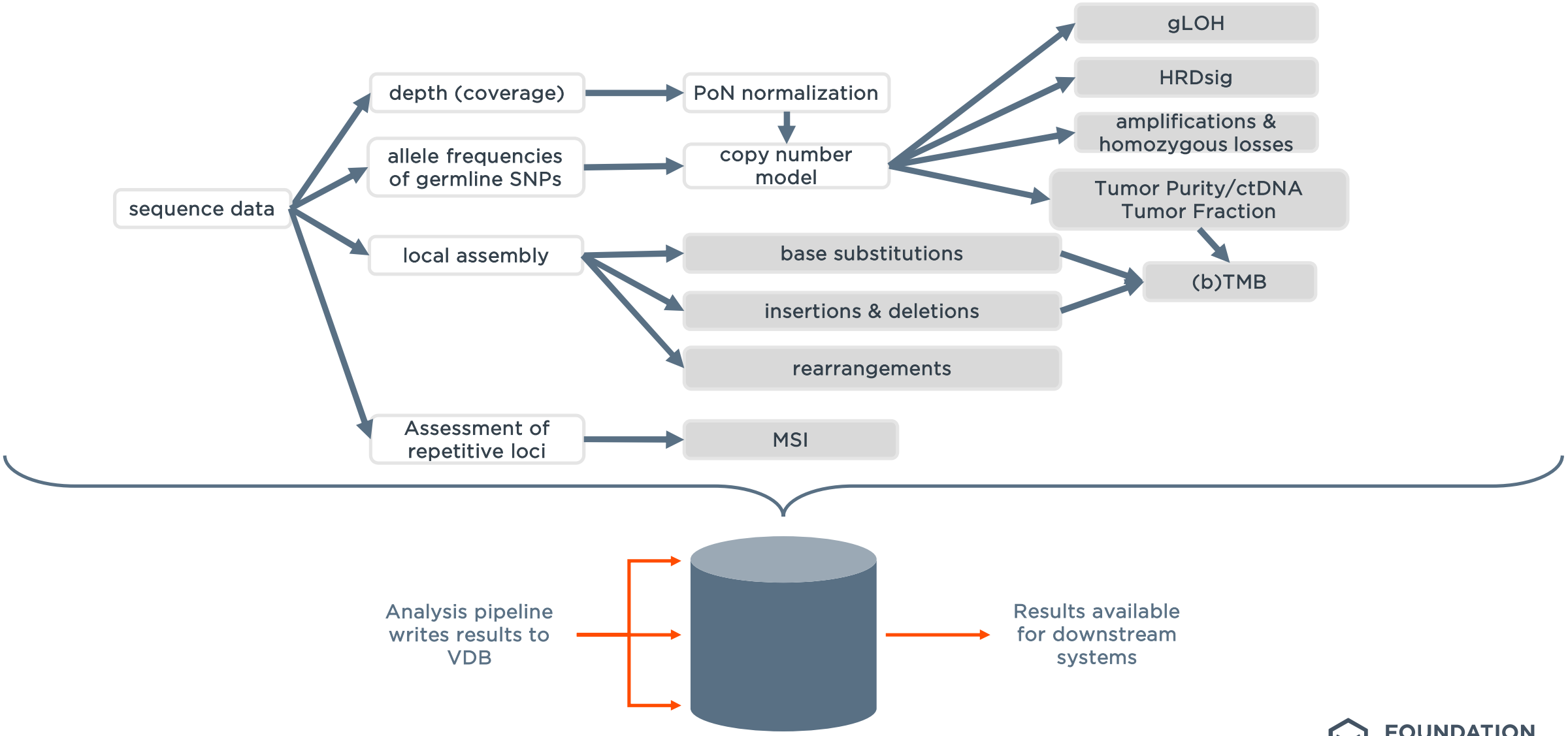
Slide 18

MG35 Could replace next slide or a different slide?
Mary Gearing; 07.09.2023

TW1 I added the R&D + Ops people working on CompBio and MR
Thomas Wieland; 08.09.2023

Fully Automated Bioinformatics Pipeline



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Clinical Reporting Curation Process

Reporting requires extensive scientific and clinical expertise and judgment

Analyze genomic alterations

- Impact on DNA/protein function
- Impact on molecular and cellular pathways

Compile evidence

- Scientific publications and conferences
- Medical experts
- Online databases (COSMIC, cBioPortal, PubMed)

Interpret in context of patient's disease

- Evidence of efficacy/lack of efficacy for approved therapies targeting recovered alteration
- Clinical trials
- Contraindications

Communicate

- Summarize therapeutic implications
- Summarize gene interpretation

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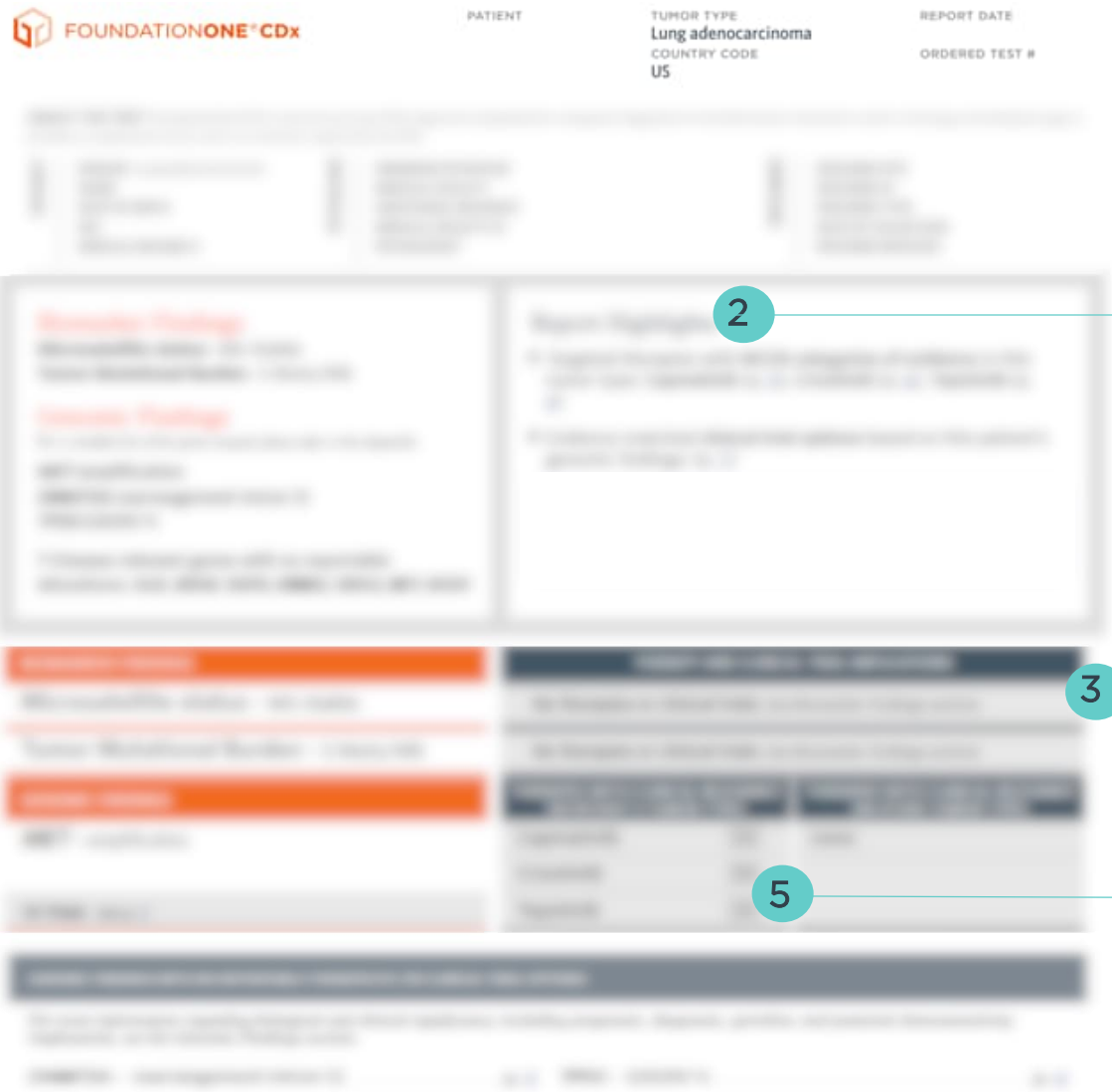
FoundationOne®CDx Professional Services - Summary Page

Example From Lung Cancer Report



1 Biomarker and Genomic Findings (Including pertinent negatives)

2 Report Highlights

3 Findings and Actionability

4 Clinical Trials

5 NCCN Categories of Evidence and Consensus

6 Findings without Reportable Therapeutic or Clinical Trial Options

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FoundationOne®CDx: Biomarker and Genomic Findings

Example From Lung Cancer Report

Biomarker Findings

- Result
- Potential Treatment Strategies (pre-clinical and clinical evidence)
- Frequency and Prognosis (disease-specific)
- Finding Summary (result, relevance)

Genomic Findings

- Gene Variant Information
- Potential Treatment Strategies: Clinical relevance
- Frequency and Prognosis: In the specimen tumor type and/or other tumor types
- Finding Summary: Gene, function, biological implication of the alteration

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Current as of February 2023.

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Cloud Architecture

Sequencing Data Analysis is Computational Resource Heavy

- July 2024
  - 13.2M Core Hours/Month = 1,500 years
  - 90 PB of data

- Complex Architecture controlled by Infrastructure as Code
  - 200+ AWS accounts
  - Several 10 Gb/s direct connections for data upload
  - Dynamically growing compute clusters
  - Heavy use of spot instances

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Data & Research

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Foundation Medicine is on a Mission to Transform Cancer Care

Our approach to precision medicine revolves around patients

CLINICAL

Genomic testing enables patient access to personalized cancer management

BIOPHARMA

Assays and data fuel better, more efficient therapeutic R&D + Companion Diagnostic (CDx) development

DATA

FoundationCore: Largest global database with 800,000+ real-world genomic profiles

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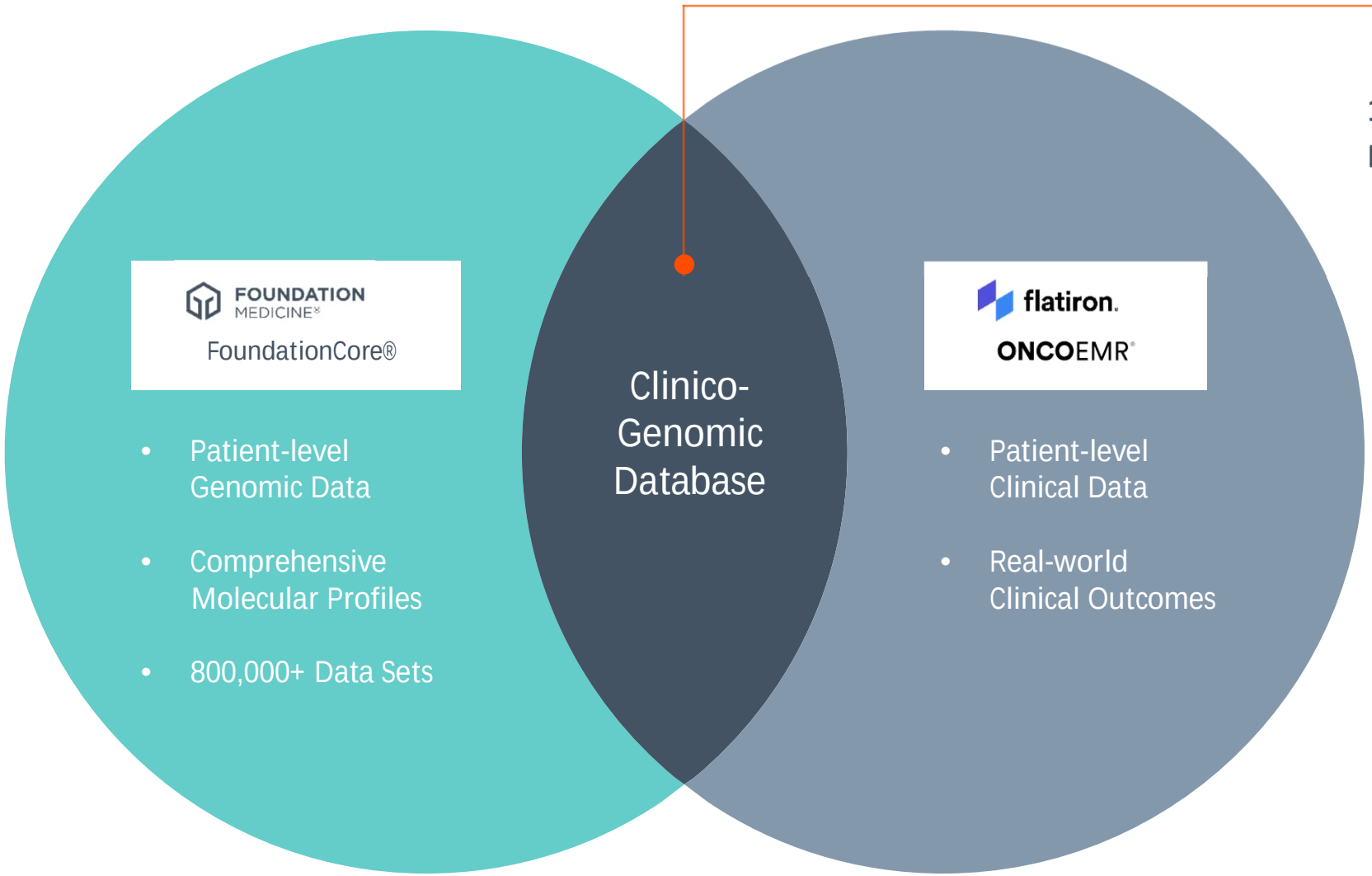
A Transformative Clinico-Genomic Database



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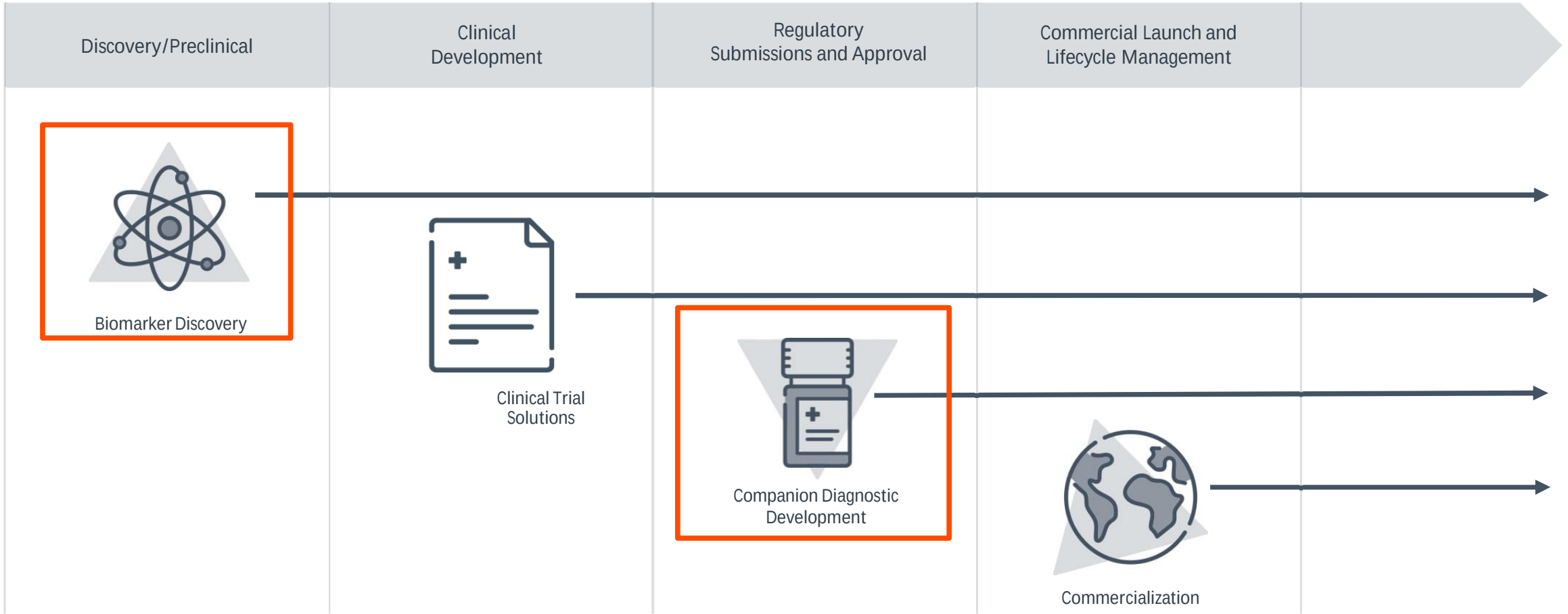
Enabling Drug Discovery, Development and Commercialization



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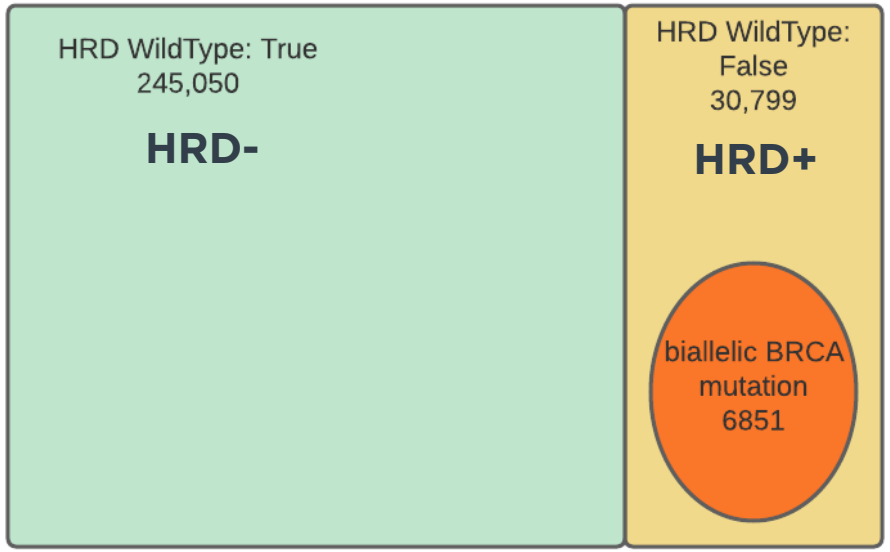
HRD Signature (HRDsig) Biomarker Development

A comprehensive scar-based copy number signature reported on FoundationOne®CDx

- Developed using artificial intelligence (AI)
- Built with a diverse set of **>100 copy number features**
- Trained using a large pan-tumor genomic database (>500,000 samples)
- Performance was examined in a set of approximated "true positive" and "true negative" samples:
  - "True positive": Biallelic *BRCA1/2*
  - "True negative": HRR gene wild-type
- Performance down to at least 20% tumor purity



HRDsig uses >100 CN features to capture the nuanced HRD phenotype, representing an improvement over gLOH

gLOH = genomic loss of heterozygosity, HRD = homologous recombination deficiency, HRR = homologous recombination repair.

Antonarakis E, et al. *Cancer Res*. 2022;82(12_supp):1249.

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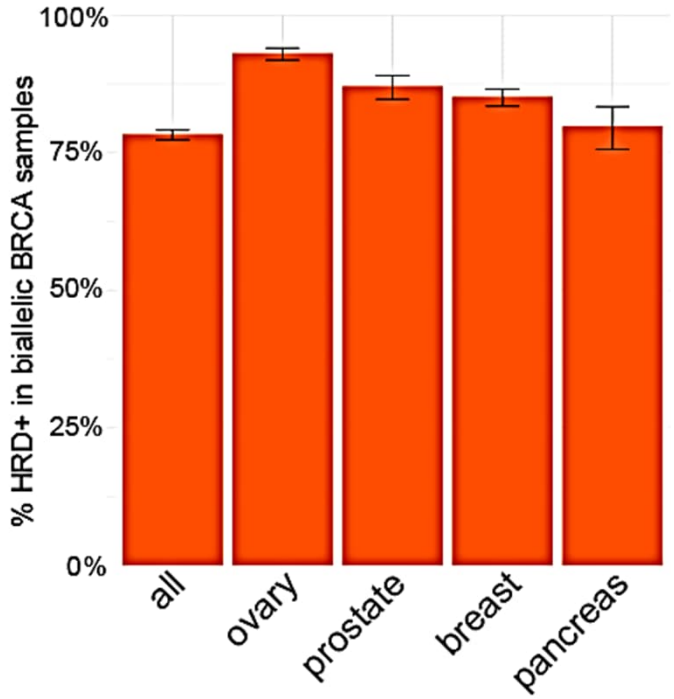
Biomarker Discovery: HRD Signature (HRDsig) Validation

A machine learning comprehensive scar-based CN signature that gives a functional HRD readout for multiple cancer types

- Does not rely on HRR mutations (can detect non-genomic mechanisms of HRD including BRCA methylation)
- Captures most biallelic *BRCA* and a subset of other HRRmut and HRRwt cases likely to truly have HRD, but distinguishes monoallelic HRR passenger mutations
- Has been analytically and clinically validated for use pan-tumor using our genomic dataset and CGDB, and through collaborative assessment of clinical trial cohorts

Able to detect majority of patients with *BRCA* biallelic loss across *BRCA*-associated tumor types



Antonarakis E, et al. *Cancer Res*. 2022;82(12_supp):1249.

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Natural History Evaluation of Clinical Studies

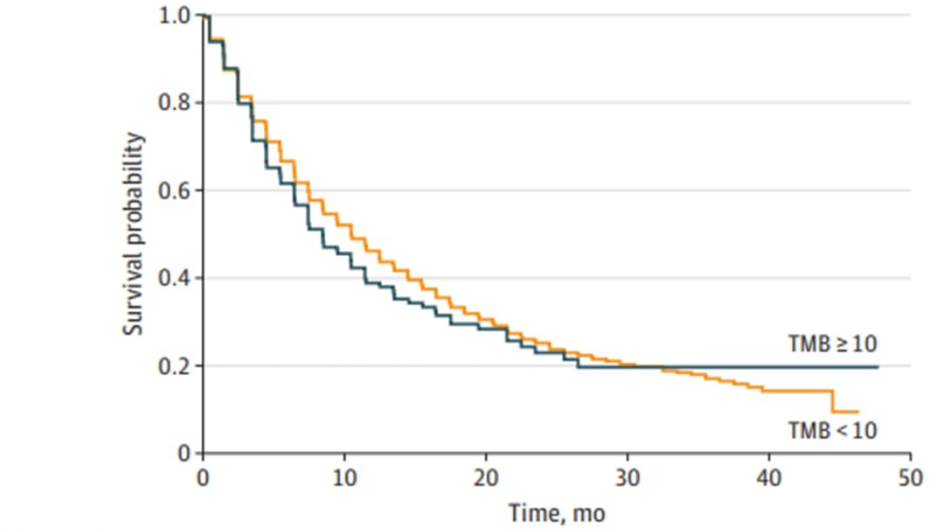
„Virtual Control Arm“

Clinical Trial > Lancet Oncol. 2020 Oct;21(10):1353-1365. doi: 10.1016/S1470-2045(20)30445-9. Epub 2020 Sep 10.

Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study

Observational Study > JAMA Netw Open. 2020 Oct 1;3(10):e2025109. doi: 10.1001/jamanetworkopen.2020.25109.

Prevalence of High Tumor Mutational Burden and Association With Survival in Patients With Less Common Solid Tumors



No. at risk						
TMB < 10	1913	552	197	79	14	0
TMB ≥ 10	285	59	21	9	5	0

1. Marabelle A et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. 2020 Oct;21(10):1353-1365. doi: 10.1016/S1470-2045(20)30445-9. Epub 2020 Sep 10. PMID: 32919526.
2. Shao C et al. Prevalence of High Tumor Mutational Burden and Association With Survival in Patients With Less Common Solid Tumors. JAMA Netw Open. 2020 Oct 1;3(10):e2025109. doi: 10.1001/jamanetworkopen.2020.25109. PMID: 33119110; PMCID: PMC7596577.

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Conclusions

1. **CGP is a key diagnostic tool**
2. **High quality results require standardization and automation**
3. **High quality diagnostic data is instrumental in R&D and drug development**

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Thank you for your attention!

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