Guideline Development for Comprehensive Genomic Tumor Testing for Cancer

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Making Cancer History®

Declaration of interests

Financial interests:

- Consulting for AbbVie Inc., Aduro BioTech Inc., Alkermes, AstraZeneca, Black Diamond Therapeutics, Calibr (a division of Scripps Research), Daiichi Sankyo Co., Debiopharm International, EcoR1 Capital, eFFECTOR Therapeutics, F. Hoffmann-La Roche, GT Apeiron Therapeutics, Genentech Inc., Harbinger Health, IBM Watson, Infinity Pharmaceuticals Inc., Jackson Laboratory, Kolon Life Science Inc., LegoChem Bio, Lengo Therapeutics Inc., Loxo Oncology Inc., Menarini Group, OnCusp Therapeutics, OrigiMed, PACT Pharma Inc, Parexel International, Pfizer Inc., Protai Bio, Samsung Bioepis Co., Seagen Inc., Tallac Therapeutics Inc., Tyra Biosciences Inc., Xencor Inc., Zymeworks Inc.
- Data Safety Monitoring Boards or Advisory Boards for Black Diamond Therapeutics, Biovica International AB, Eisai Co., FogPharma, Immunomedics, Inflection Biosciences, Karyopharm Therapeutics, Loxo Oncology Inc., Mersana Therapeutics Inc., OnCusp Therapeutics, Puma Biotechnology Inc., Protai Bio, Sanofi, Seagen Inc., Silverback Therapeutics, Spectrum Pharmaceuticals Inc., Theratechnologies Inc., Zentalis Pharmaceuticals
- Investigator for Aileron Therapeutics, AstraZeneca, Bayer Healthcare, Calithera Biosciences Inc., Curis Inc., CytomX Therapeutics Inc.,Daiichi Sankyo Co., Debiopharm International, eFFECTOR Therapeutics, Genentech, Guardant Health, Klus Pharma, Novartis,Taiho Pharmaceutical Co.
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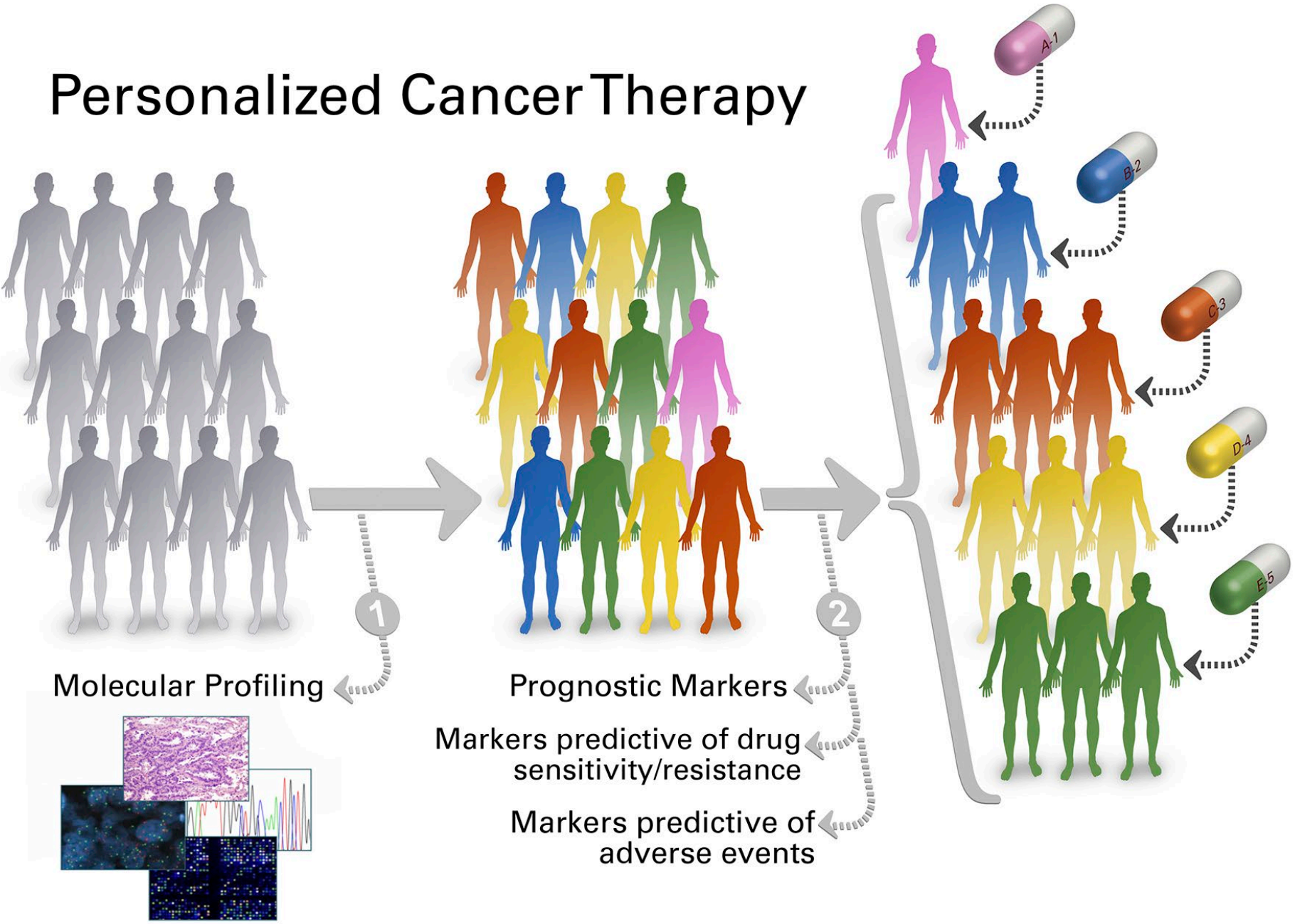
  Cholangiocarcinoma Foundation

Personalized Cancer Therapy



Personalizedcancertherapy.org

Areas where Guidelines are Needed/helpful

- Who needs somatic genomic testing?
  - Diagnosis, prognosis and therapy selection
- What kind of testing?
  - Small panel, larger panels, whole exome vs whole genome
  - DNA vs DNA+RNA
- Tumor only vs tumor+ normal- what should be returned?
- Germline testing/reporting
  - Future risk- implication for family
  - Therapy selection
- Pharmacogenomics
- Reporting /annotations
- Decision support to interpret results

Why Do We Need Guidelines?

- Best oncologic practice
  - Ensure all patients that benefit from testing are offered testing
    - Patients with diseases with approved genomically matched therapies should get appropriate testing
  - Ensure all patients have access to treatment for at least agents with Level 1 evidence
- Guidelines and impact on Coverage
  - All patients that may benefit from testing should get tested
  - Access to treatments as well as testing
- Limited study into disparities in care as pertaining to genomically informed therapy
  - Differences in access to testing?
  - What testing is offered?
  - Whether actionable alterations are acted upon
  - Access to genomically-matched trials

Genomically-Informed Targeted Therapy

- Identifying genomic alterations that are
  - Drivers of tumor growth and progression
  - Targetable directly or indirectly with approved or investigational agents

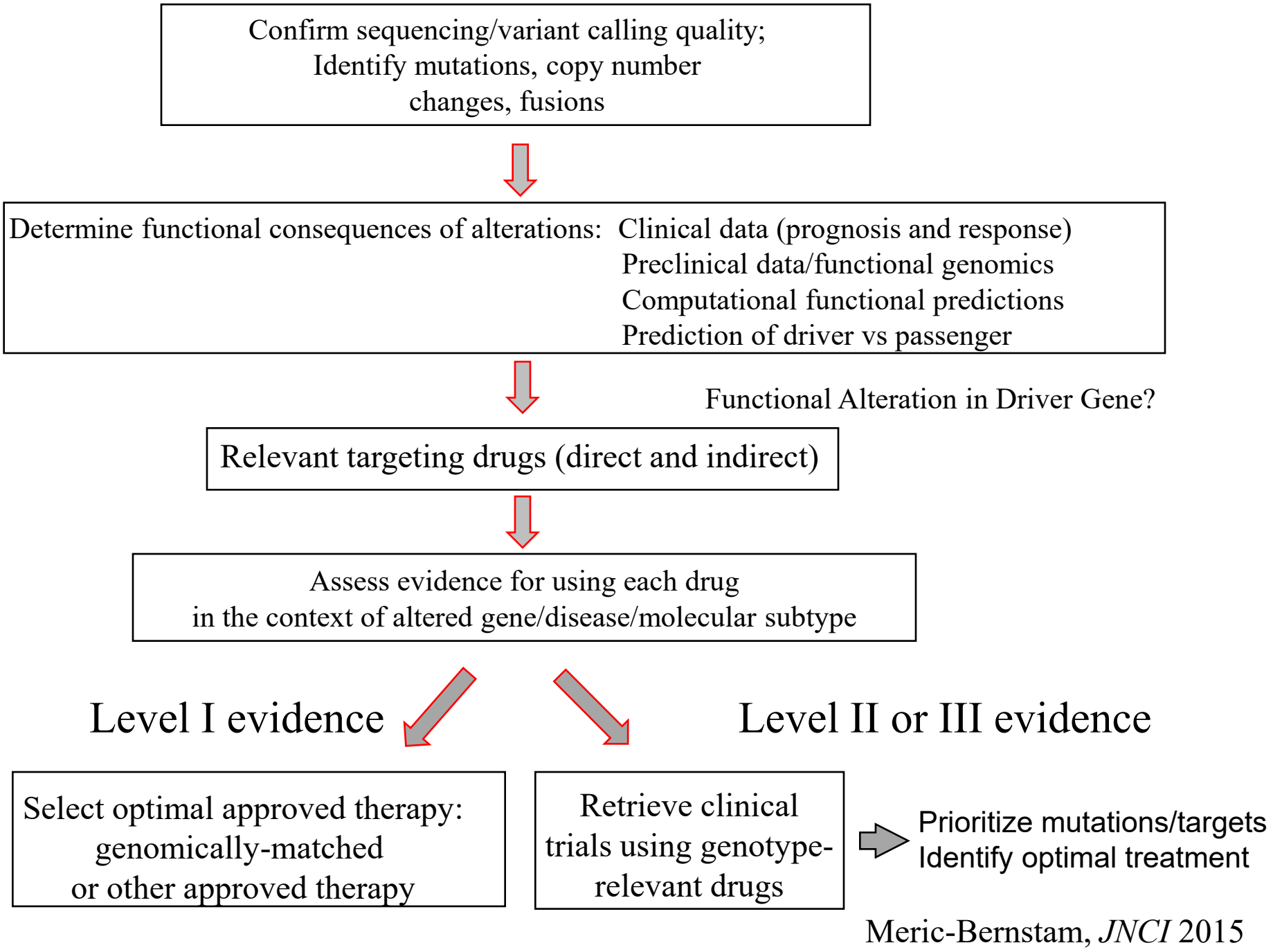
- Mutations
  - Somatic and germline
  - SNVs and indels
- Copy number changes
  - Amplifications/deletions
- Fusions

Targeting Actionable Genes

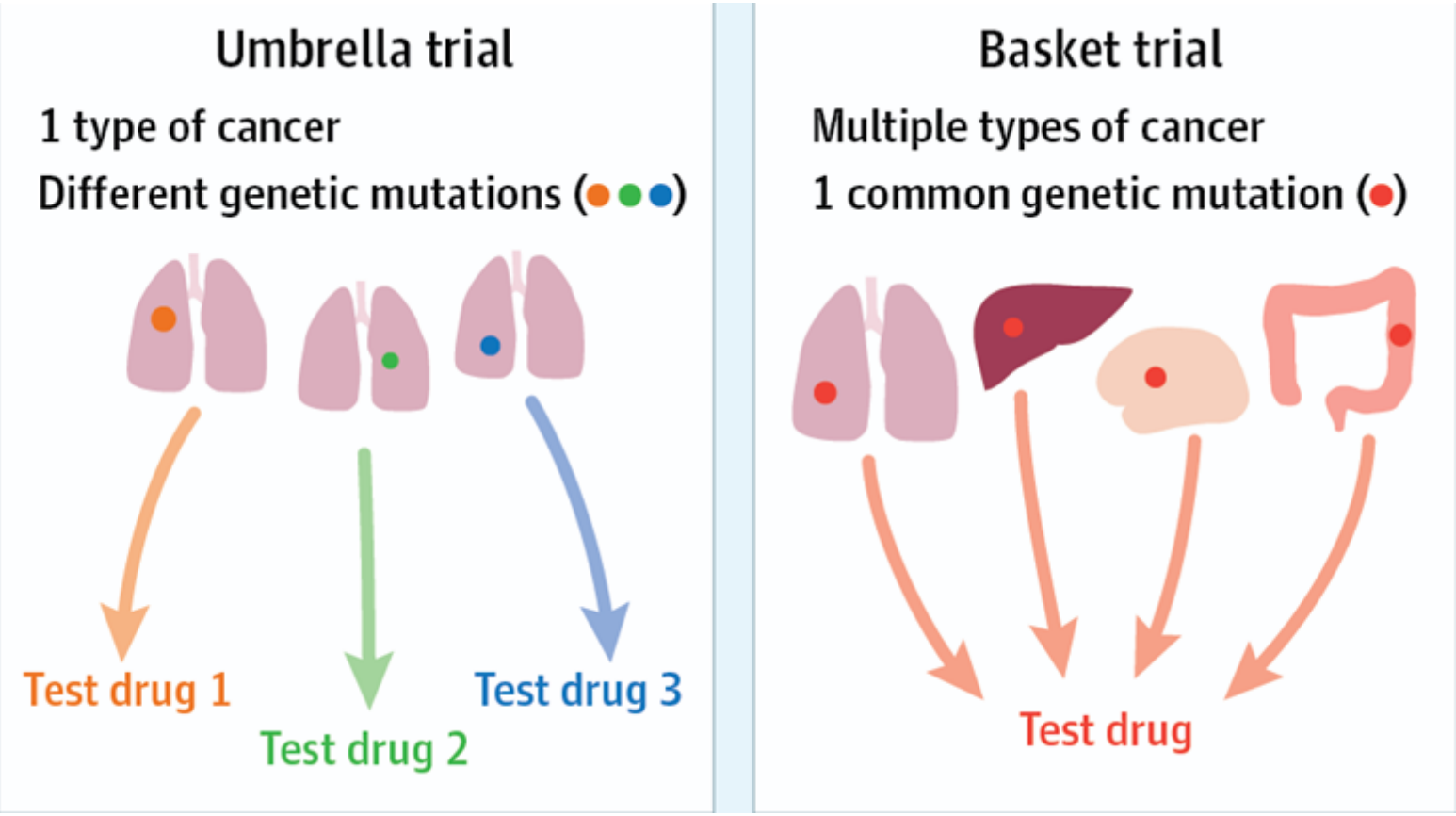
A genomic alteration can be considered "actionable" if it:

- predicts therapy response (sensitivity or resistance)
- affects the function of a cancer-related gene, and can be targeted directly or indirectly with approved or investigational therapies.
- is a specific eligibility criteria for enrollment onto genotype-selected trials,
- has demonstrated the ability to establish diagnosis or influence prognosis
- is a germline alteration that predicts drug metabolism and/or adverse effects
- is a germline alteration that predicts future risk of cancer or other diseases (usually considered more "actionable" if prevention or screening with early treatment is feasible)

Meric-Bernstam, *JNCI* 2015


Confirm sequencing/variant calling quality;
Identify mutations, copy number
changes, fusions
Determine functional consequences of alterations: Clinical data (prognosis and response)
Preclinical data/functional genomics
Computational functional predictions
Prediction of driver vs passenger
Functional Alteration in Driver Gene?
Relevant targeting drugs (direct and indirect)
Assess evidence for using each drug
in the context of altered gene/disease/molecular subtype
Level I evidence
Level II or III evidence
Select optimal approved therapy:
genomically-matched
or other approved therapy
Retrieve clinical
trials using genotype-
relevant drugs
Prioritize mutations/targets
Identify optimal treatment
Meric-Bernstam, *JNCI* 2015

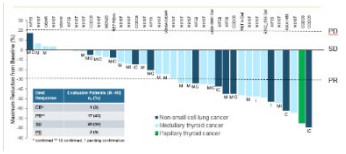
Increasing Number of Genomically Informed Trials



West, JAMA Oncology, 2017

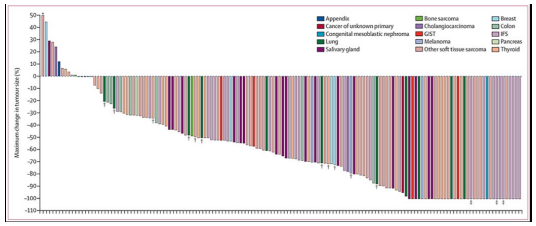
Many Successes in Targeted Therapy

RET fusions



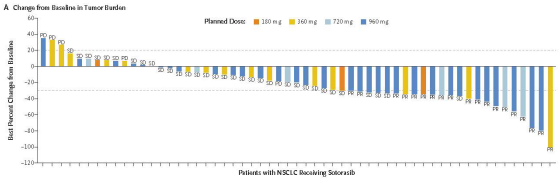
Subbiah et al, *Cancer Discovery*, 2019

NTRK fusions



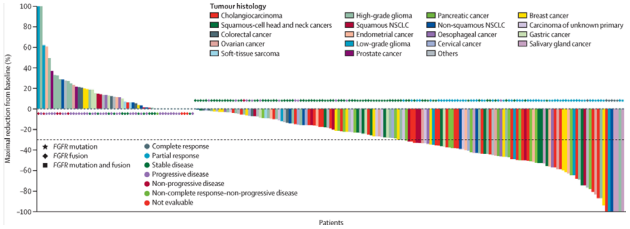
Hong et al , Lancet Oncology 2020

KRAS G12C



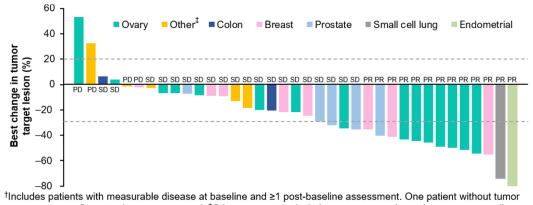
Hong et al, *NEJM* 2020

FGFR



Pant, *Lancet Oncology* 2023

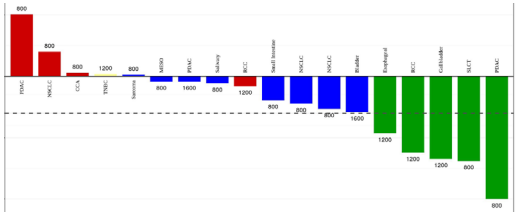
p53 Y220C



†Includes patients with measurable disease at baseline and ≥1 post-baseline assessment. One patient without tumor measurement at first scan is not represented. ‡Other tumor types include sarcoma, esophageal cancer, germ cell tumor, pleomorphic rhabdomyosarcoma, and urothelial cancer. Data cut-off: 05 Sept 2023.
BID, twice daily; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease; WT, wildtype.

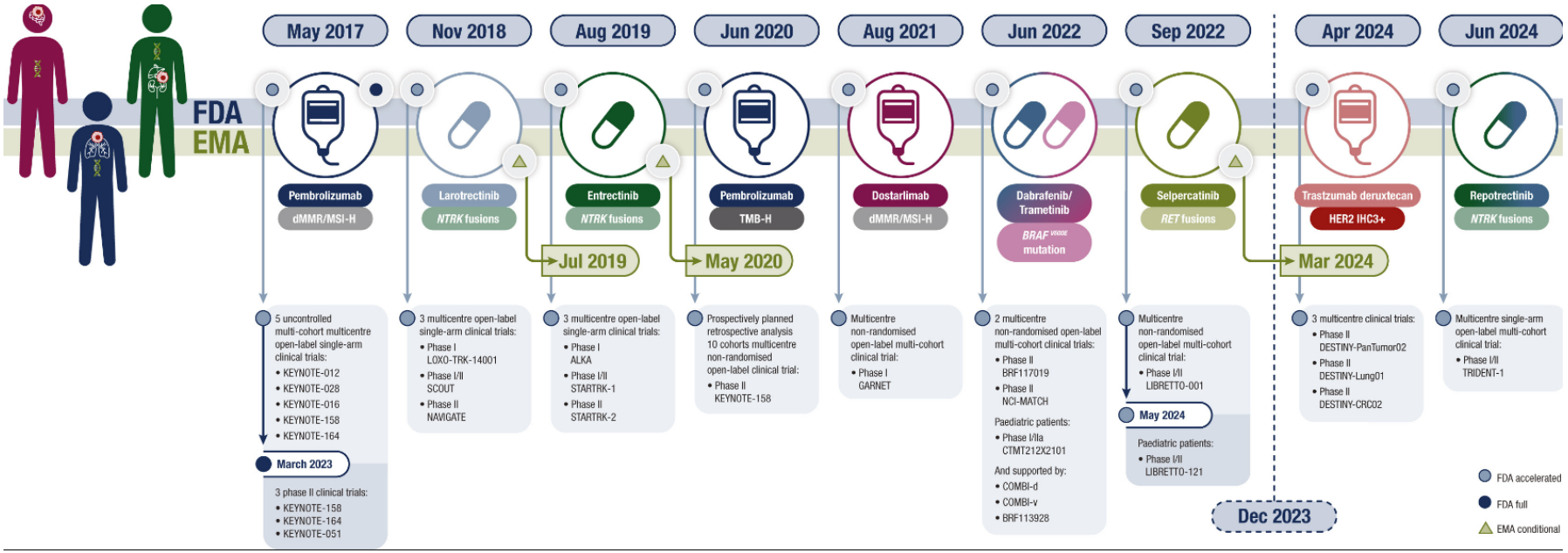
Shram …Dumbrava, *AACR-NCI-EORTC* 2023

MTAP



Rodon *et al, AACR-NCI-EORTC* 2023

Tumor Agnostic Therapies



Westphalen et al *Ann Onc* 2024

Clinical Utility in Genomic Testing

- Tumor types
  - Tumor types with FDA-approved genomically-matched therapy for that disease
  - Likelihood of finding actionable alterations
- Not all alterations on genomic alterations in actionable genes are actionable
- Different drugs may have differential effects on different mutations
  - Patients with certain SNVs may benefit from specific inhibitors
  - Certain inhibitors may work better in certain variants
- Co-alterations matter
- Different adaptive responses in different tumor types (eg BRAF in CRC)
- Access to genomically-matched therapy
  - Approved and clinical trials
  - Disparities to access to trials- availability as well as ability to participate

Challenges in Guideline Development for Genomic Testing

- Many oncology guidelines based on level 1 data from randomized controlled trials
- No trials of NGS vs not
- Few randomized trials pf genomically matched therapy vs not
  - very difficult to do as there is no equipoise
- The few trials that have been done have not shown major impact of genomically matched therapies but most of these trials did not include current state of the art therapies

- Putting together a guideline committee with domain expertise but no conflicts
- Work without funding

ASCO special article

Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion

Debyani Chakravarty, PhD[1]; Amber Johnson, PhD[2]; Jeffrey Sklar, MD, PhD[3]; Neal I. Lindeman, MD[4]; Kathleen Moore, MD[5]; Shridar Ganesan, MD, PhD[6]; Christine M. Lovly, MD, PhD[7]; Jane Perlmutter, PhD[8]; Stacy W. Gray, MA, MD[9]; Jimmy Hwang, MD[10]; Christopher Lieu, MD[11]; Fabrice André, MD, PhD[12]; Nilofer Azad, MD[13]; Mitesh Borad, MD[14]; Laura Tafe, MD[15]; Hans Messersmith, MPH[16]; Mark Robson, MD[1]; and Funda Meric-Bernstam, MD[2]

- Patients with metastatic or advanced cancer should undergo genomic sequencing in a certified laboratory if the presence of one or more specific genomic alterations has regulatory approval as biomarkers to guide the use of or exclusion from certain treatments for their disease.
- Site-agnostic approvals for any cancer with a high tumor mutation burden, mismatch repair deficiency, or neurotrophic tyrosine receptor kinase (NTRK) fusions provide a rationale for genomic testing for all solid tumors
  - this was prior to RET and BRAF pantumor approvals

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group

M. F. Mosele[1,2], C. B. Westphalen[3], A. Stenzinger[4], F. Barlesi[1,2,5], A. Bayle[5,6,7,8], I. Bièche[9], J. Bonastre[7,8], E. Castro[10], R. Dienstmann[11,12,13], A. Krämer[14,15], A. M. Czarnecka[16,17], F. Meric-Bernstam[18], S. Michiels[7,8], R. Miller[19,20], N. Normanno[21], J. Reis-Filho[22†], J. Remon[2], M. Robson[23], E. Rouleau[24], A. Scarpa[25], C. Serrano[11], J. Mateo[11] & F. André[1,2,5*]

Methods:
ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) considering cost-effectiveness and accessibility

Focus on ESCAT level I, since they are the key determinants for recommending the use of NGS for routine practice within specific cancer types.
In addition, it was unanimously agreed to report ESCAT level II genomic alterations to facilitate patient enrolment in clinical trials and promote drug development.

2024 ESMO update after 2020 recommendations

- ESMO recommends running tumor NGS in advanced non-squamous nonsmall-cell lung cancer, prostate cancer,colorectal cancer, cholangiocarcinoma, and ovarian cancer.

- In 2024 updated report, expansion to encompass patients with advanced breast cancer and rare tumours such as gastrointestinal stromal tumours, sarcoma, thyroid cancer, and cancer of unknown primary.

- ESMO recommends carrying out NGS to detect tumor-agnostic alterations in patients with metastatic cancers where access to matched therapies is available.

Mosele et al, Ann Onc, 2024

Summary

- Guideline development for genomic testing is hard in part because of lack of high quality data
- At this time randomized trials of genomic testing vs not or genomically matched therapy vs not is not feasible or ethical
- There is a rapid growth in genomically informed therapies

- Evolving areas:
  - Comprehensive testing
  - Liquid biopsies for response monitoring and MRD
  - Emerging decision support including AI applications

- Further study is needed into how to streamline guideline development and ensure guidelines are translated into the clinic

Acknowledgments

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Disease Champions

Pathology

THANK YOU!

Questions/comments/collaborations/concepts:

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