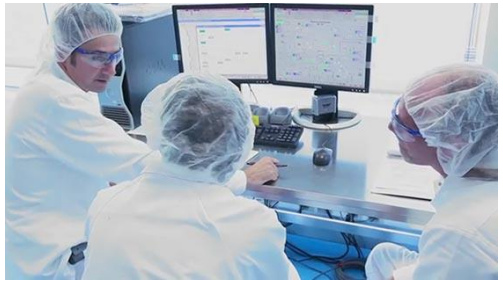
Studien 2019: von der randomisierten Studie zu Big-Data und personalisierter Medizin

PD. Dr. Johannes Pleiner-Duxneuner

Lasting know-how and strong partnerships put Roche in a unique position to co-create a personalised healthcare ecosystem

Pharma | Roche | Diagnostics

FOUNDATION MEDICINE | flatiron | NAVIFY®



Research & Development | **Digital Health** | **Comprehensive Genomic Profiling**

FoundationOne Services CDx, Heme, Liquid

Targeted Therapy

Alectinib (ALK)
Entrectinib (NTRK, ROS1)
Erlotinib (EGFR)
Cobimetinib (MEK)
Vemurafenib (BRAF)
Atezolizumab (PD-L1, TMB – high, MSI)
Trastuzumab, Pertuzumab, T-DM1/Trastuzumab Emtansine (HER2)
Vismodegib (PTCH1, SMO)
Ipatasertib (AKT, PI3K, PTEN)
Idasanutlin (MDM2)
GDC-0077 (PI3K)
Belvarafenib (pan-RAF)
iNeST (Personalized Cancer Vaccine)

Navify – Tumor Board

Avenio – targeted, expanded, surveillance

FMI kit

Nafivy - Mutation Profiler

Digital Pathology

Ventana (IHC)

COBAS testing

Current and future offerings of Roche Pharma and Diagnostics

Overview on the Foundation Portfolio

	FOUNDATIONONE®CDx[1]	FOUNDATIONONE®LIQUID[2]	FOUNDATIONONE®HEME[3] (ab Q4 2019)
Indikationen	Alle soliden Tumore	Flüssigbiopsie (ctDNA) - alle soliden Tumore	Hämatologische Erkrankungen, Sarkome*
Specimen	FFPE Gewebe	Vollblut	FFPE Gewebe, Vollblut, Knochenmarkaspirat
Anzahl der analysierten Gene	324 (DNA)	70 (DNA)	405 (DNA) 265 (RNA)
Biomarker Immuntherapie	MSI and TMB	MSI	MSI and TMB
Companion diagnostic	FDA-approved CDx für 18 Target Therapies		

* Soft tissue and bone

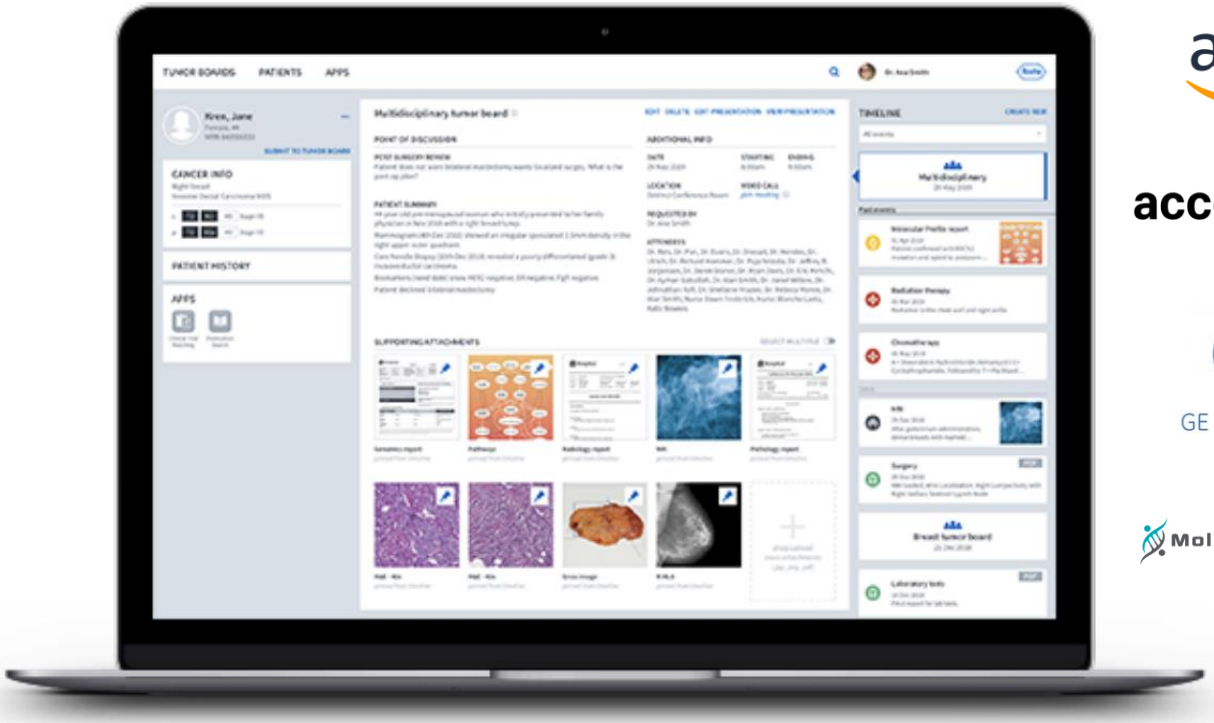
ctDNA: circulating tumour DNA; FFPE: formalin-fixed paraffin-embedded tissue; MSI: microsatellite instability; TMB: tumor mutational burden.

1. Foundation Medicine, Inc. (2018) FoundationOne CDx Technical Specifications;
2. Foundation Medicine, Inc. (2018) FoundationOne Liquid Technical Specifications;
3. Foundation Medicine, Inc. (2017) FoundationOne Heme Technical Specifications and Test Overview.

FOUNDATION MEDICINE® | Roche

NAVIFY Tumor Board & Apps

First workflow product introduced in 2017



aws

accenture

GE Healthcare

MolecularMatch

NAVIFY

Roche

Clinical Decision Support apps

The clinical decision support apps ecosystem is secured and fully integrated with NAVIFY Tumor Board.

NAVIFY
Clinical Trial Match app*

Easily search the largest international trial registries, including ClinicalTrials.gov, European Medicines Agency, Japan Medical Association Center for Clinical Trials, etc.

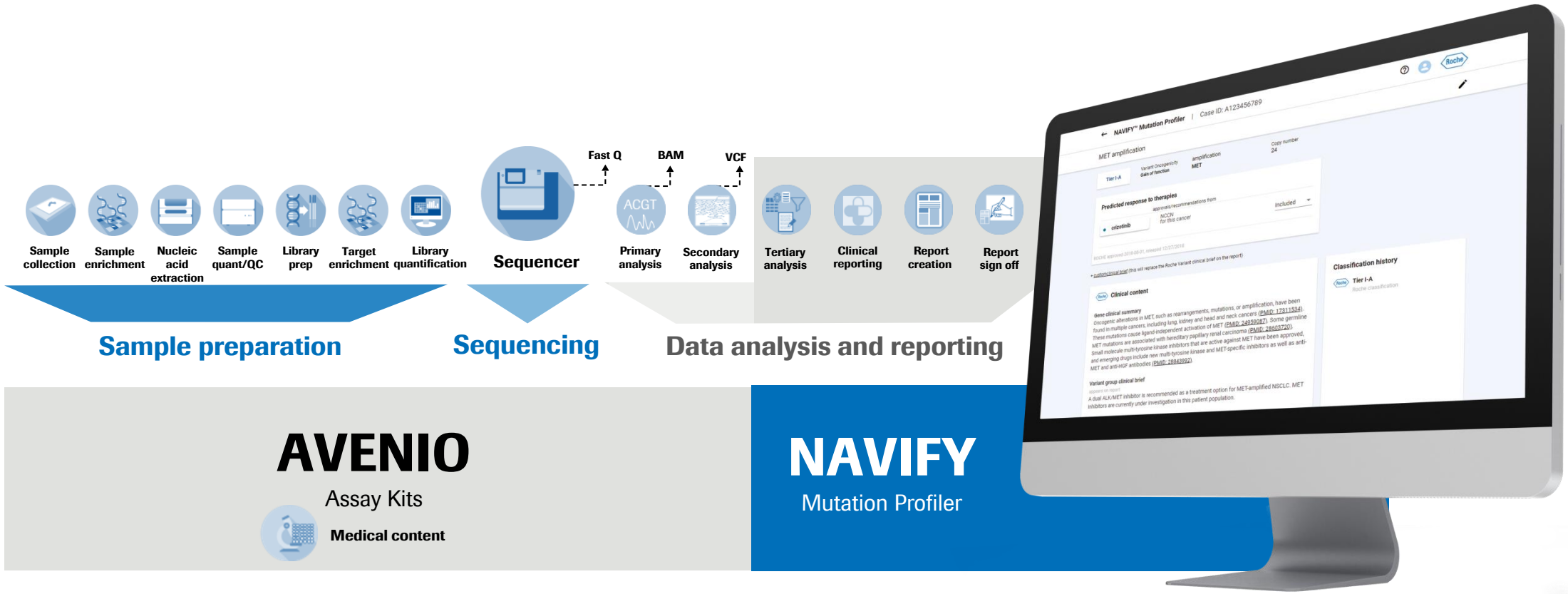
NAVIFY
Publication Search app*

Effortlessly search more than 300,000 publications across PubMed, American Society of Clinical Oncology and American Association of Cancer Research.

*) Powered by Molecular Match

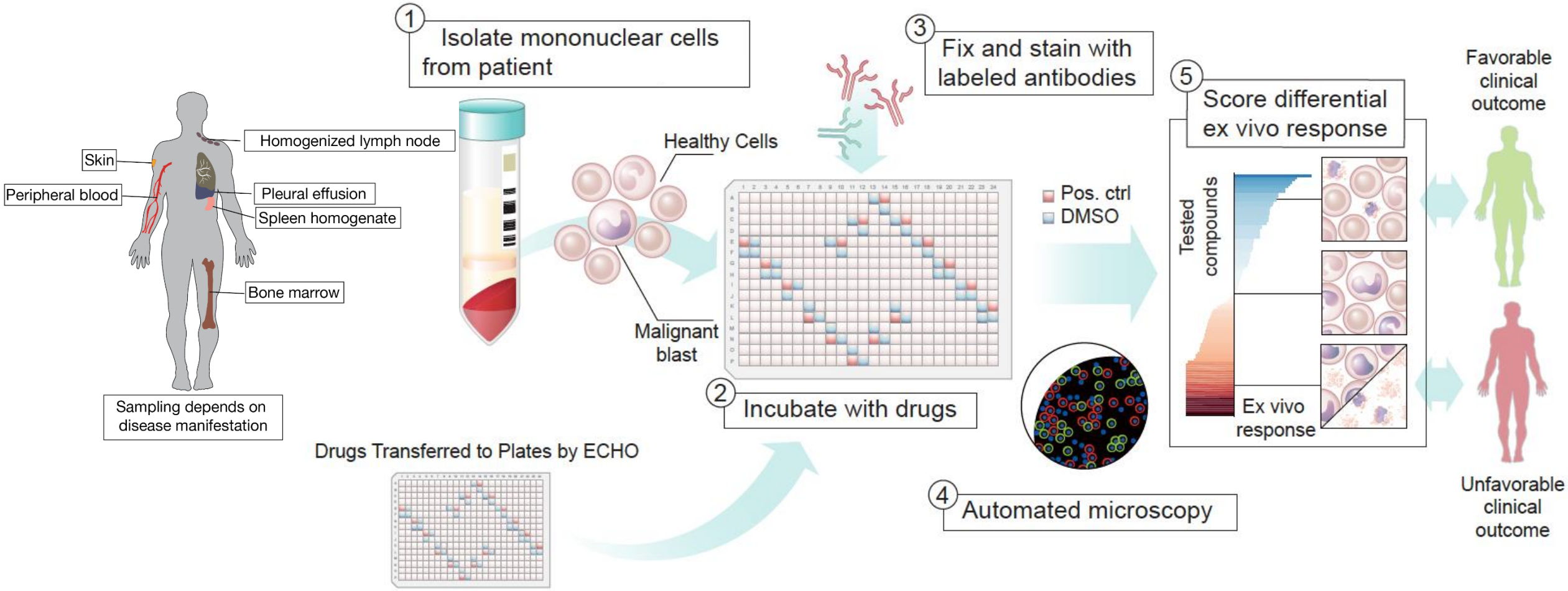
https://www.navify.com/tumorboard/

NAVIFY Mutation Profiler and NAVIFY Trial Match app
Enabling personalised cancer care



https://www.navify.com/tumorboard/

The future?
Image-based ex-vivo drug screening: Pharmacoscopy

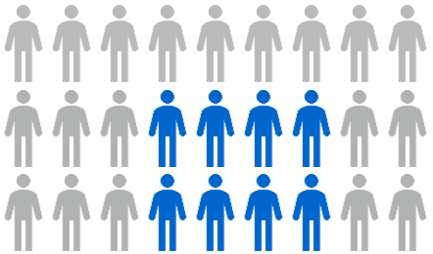
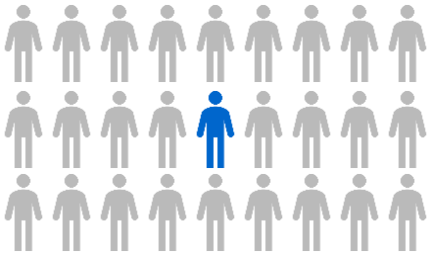


Snijder B, et al. Lancet Haematol. 2017 Dec;4(12):e595-e606

FOUNDATION MEDICINE® | Roche

The future of medicine is personalized

Improve outcomes by choosing treatments based on the outcomes of profiling

	Blockbuster Medicines	Targeted therapies	Personalised treatments
			
Target population	Large: unspecified	Medium: sub-group	Small: individual patient
Diagnostics	Histology, no specific biomarkers	Single disease marker, e.g. only *EGFR* or *BRCA1/2*	Comprehensive NGS & response and resistance monitoring
Treatment	One medicine fits all	Targeted agents	Personalised combos of targeted & CIT agents

CIT: cancer immunotherapy; NGS: next-generation sequencing.

1. Agyeman, A.A. and Ofori-Asenso, R. (2015) *J Pharm Bioallied Sci* 7:239–44; 2. Bode, A.M., et al. (2018) *npj Precision Oncol* 2:11; 3. Moscow, J.A., et al. (2018) *Nat Rev Clin Oncol* 15:183–92.

Lungen Krebs

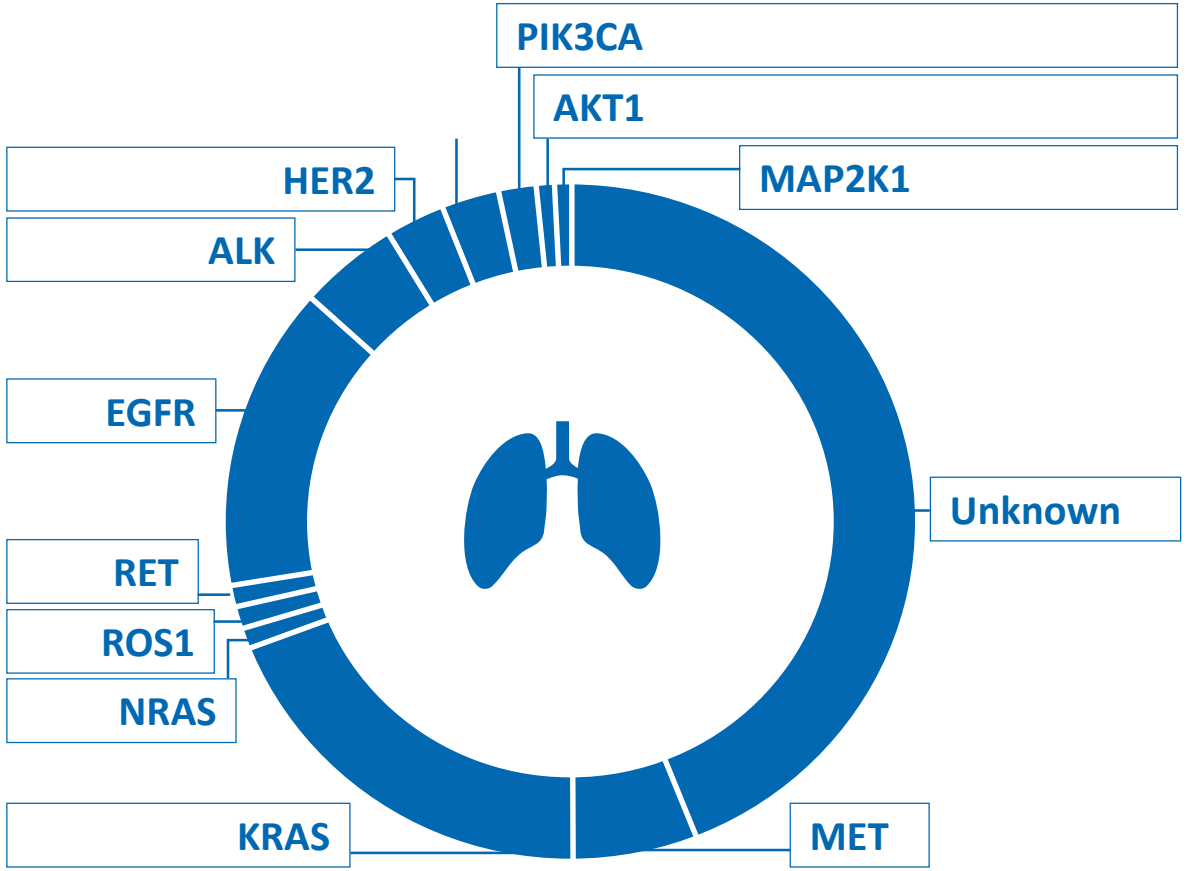
2000

Klein-zellig

Nicht-kleinzellig

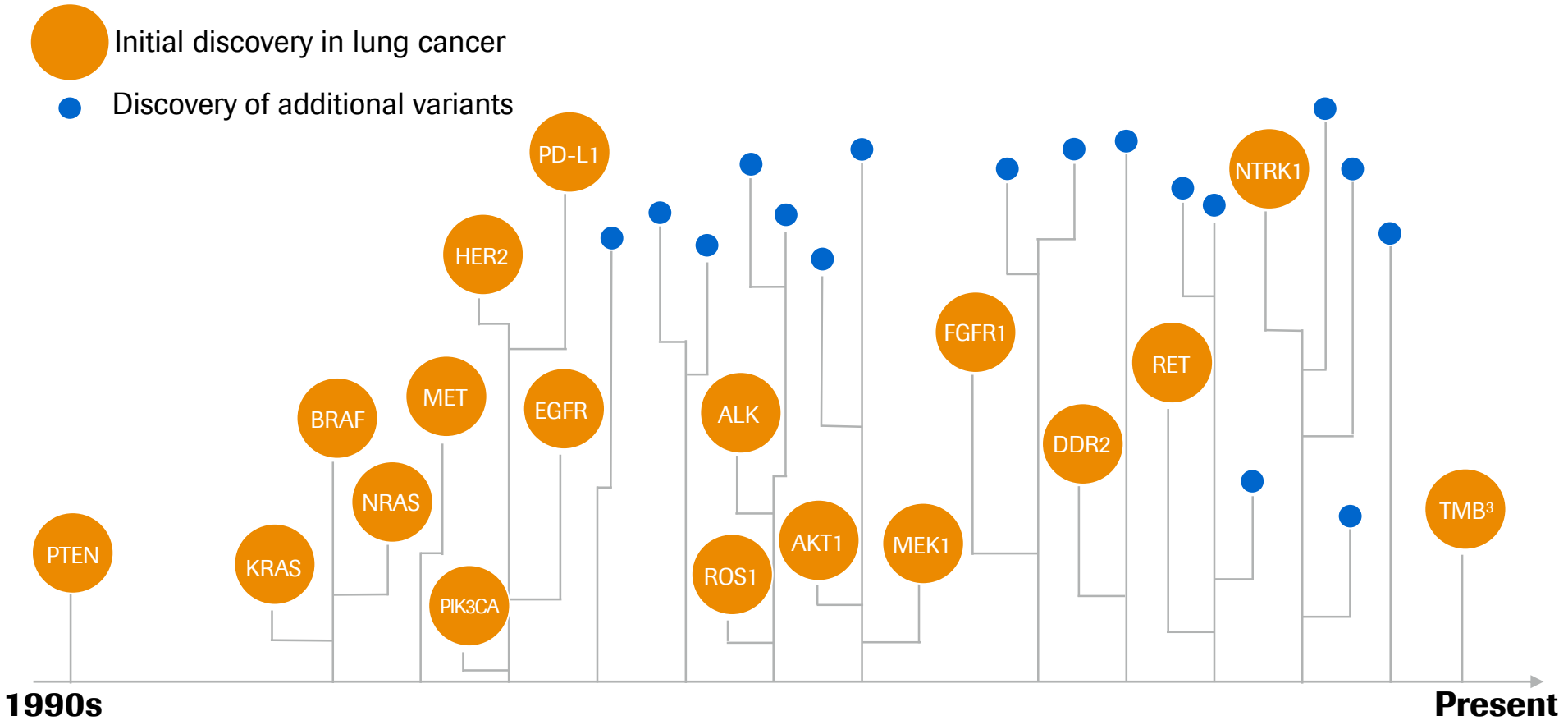
- **Adeno**
- **Plattenepithel**

2019



Current Focus Oncology

Lung Cancer: oncogenic drivers and related drug approvals



2003 / 2004
1st EGFR inhibitors
(gefitinib, erlotinib)[1]

2011
1st ALK inhibitor
(crizotinib)[2]

2016
1st ROS1 inhibitor
(crizotinib)[3]

2017
1st pan-tumour drug
(pembrolizumab▼)[4,5]

2018
1st NTRK inhibitor
(larotrectinib)[6]

Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your respective local office Merck Sharp & Dohme B.V: Pembrolizumab. 1. Drugs.com. Accessed August 2019. Available from https://www.drugs.com/history/; 2. Kazandjian D., et al. (2014) *Oncologist* 19: e5–e11; 3. FDA expands use of crizotinib. Accessed September 2019. Available from https://www.drugs.com/newdrugs/fda-expands-xalkori-crizotinib-ros-1-positive-non-small-cell-lung-cancer-4354.html; 4. Darvin P., et al. (2018) *Experimental & Molecular Medicine* 50:165. 5. FDA.gov. Accessed August 2019. Available from https://www.fda.gov/news-events/press-announcements/fda-approves-first-cancer-treatment-any-solid-tumor-specific-genetic-feature; 6. FDA.gov. Accessed September 2019. Available from https://www.fda.gov/news-events/press-announcements/fda-approves-oncology-drug-targets-key-genetic-driver-cancer-rather-specific-type-tumor. Graphic adapted from The Lung Cancer Project 2019. Accessed August 2019 at www.thelungcancerproject.org

Challenges in the Implementation of Personalized Medicine

Lack of genomic testing usage (mainly in the community-based practice)[1-3]

- Access and reimbursement of testing
- Awareness of testing and decision support for treating physicians

Unavailability of treatments suggested by genomic profiling[4-6]

Drug access
- Label (on-label vs indicated in other cancer types)
- Cost

Clinical trial access
- Physical proximity
- Trial design

Complexity and size of genomic profiling results[7]

Data handling and interpretation

Challenges in designing appropriate trials adapted to the precision medicine paradigm[8]

Types of trial designs (e.g.: umbrella, basket designs)

Lack of evidence clearly demonstrating the usefulness of genomic profiling in improving patient care[9]

Challenging for physicians and authorities to remain up-to-date with the scientific knowledge[10]

1. Eisenberg, R. and Varmus, H. (2017) *Science* 358:1133-4; 2. Yan, L. and Zhang, W. (2018) Cancer Commun 38:6; 3. Bunn, P.A. Jr and Aisner, D.L. (2018) *JAMA* 320:445–6; 4. Burris, H. A. et al, ASCO 2018 S102; 5. Trédan, O., et al. (2017) ASCO Abstract #LBA100; 6. Sohal, D.P.S., et al. (2016) *J Natl Cancer Inst* 108:djv332; 7. Mullane, M.P., ASCO 2018, Monday 4 June, 11:50, S100a; 8. Westin, S. N. ASCO 2018 S100bc. 9. Fernandez, M. et al., (2017) *N Engl J Med* 376:95-97. 10. 2018 *ASCO Educational Book* p. 647 and 699.

Challenges in the Implementation of Personalized Medicine

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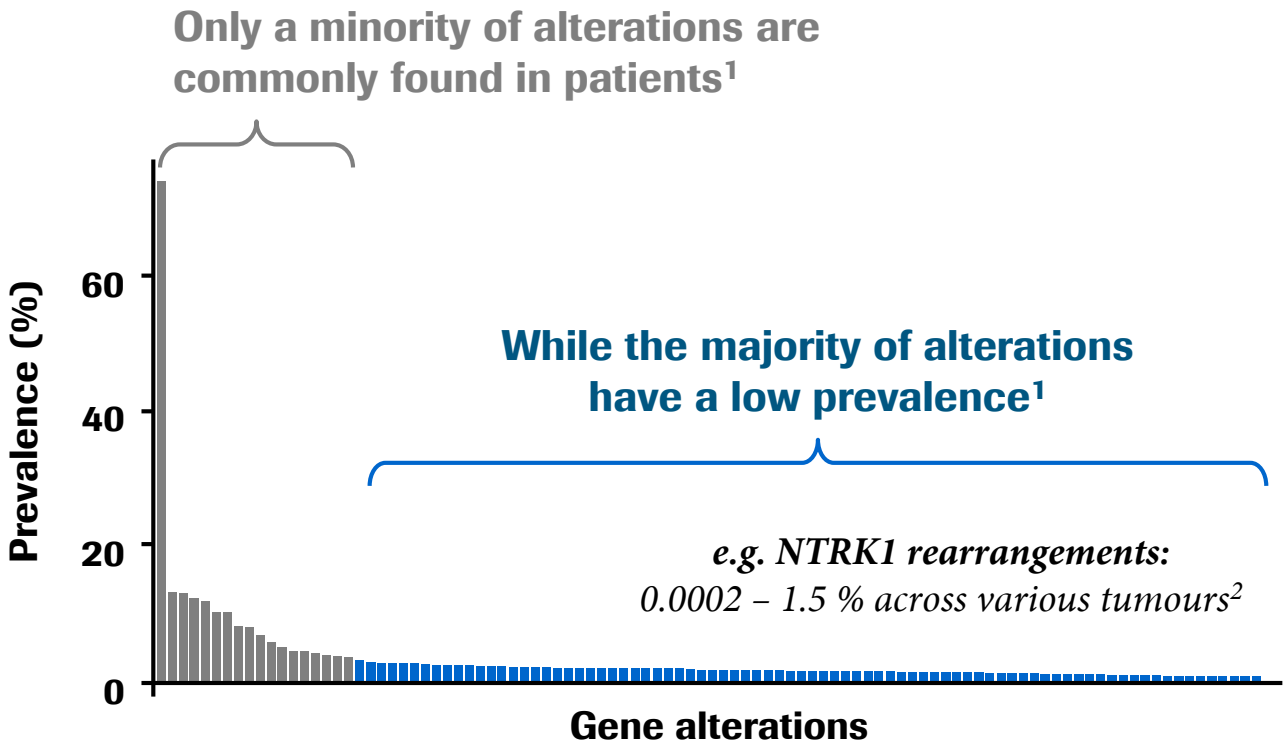
Low prevalence of distinct molecular subtypes mandates new evidence generation paths



PHC-focused trial designs[3,4]

- Increase the number of patients able to receive the right therapeutics and to participate in trials
- Accelerate timelines and increase the likelihood of accurately determining any benefit while complying more quickly with regulatory requirements

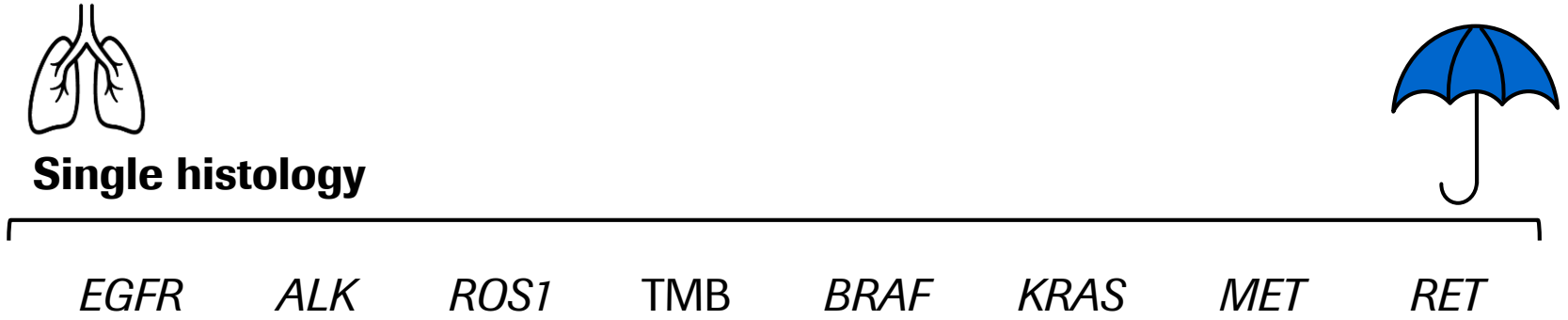
RWD[5]

- Capture the experience of the majority of cancer patients, as compared to only the <5% who have the opportunity to participate in clinical trials

PHC: personalised healthcare; RWD: real-world data.

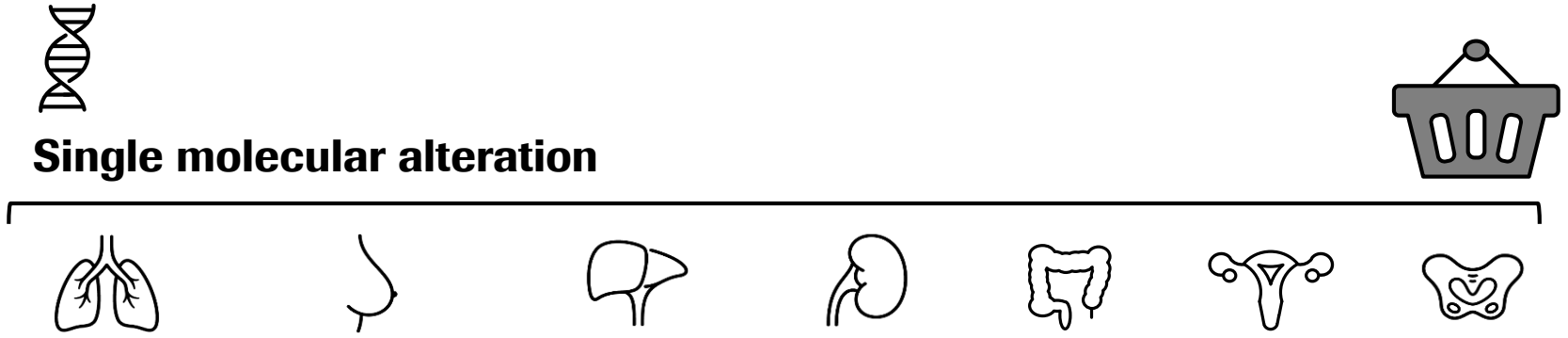
1. Data on File. FMI data base query; 2. Gatalica, Z., et al. (2019) *Mod Pathol* 32:147–53; 3. Garralda, E., et al. (2019) *Mol Oncol* 13(3):549-557; 4. Burd, A., et al. (2019) *Blood Adv* 23; 3(14): 2237–2243; 5. Booth, C.M., et al. (2019) *Nat Rev Clin Oncol* 16:312–25.

Umbrella and Basket trials



Study of **multiple genomic alterations** linked to targeted therapies in a **single histology**

- ALCHEMIST
- FOCUS4
- Lung-MAP (SWOF S1400)



Study of a **single marker** matched to a targeted therapy across **multiple histologies**

- Pediatric NCI-Match
- Signature (Novartis)
- AcSe
- CREATE

Umbrella and basket trials can incorporate an adaptive design – for example, being able to add other histologies, biomarkers, endpoints or new arms as knowledge becomes available

Dienstmann, R., et al. (2015) *Mol Oncol* 9:940–50; Burd, A., et al. (2019) *Blood Adv* 3:2237–43.

FDA approvals based on data from non-randomised trials

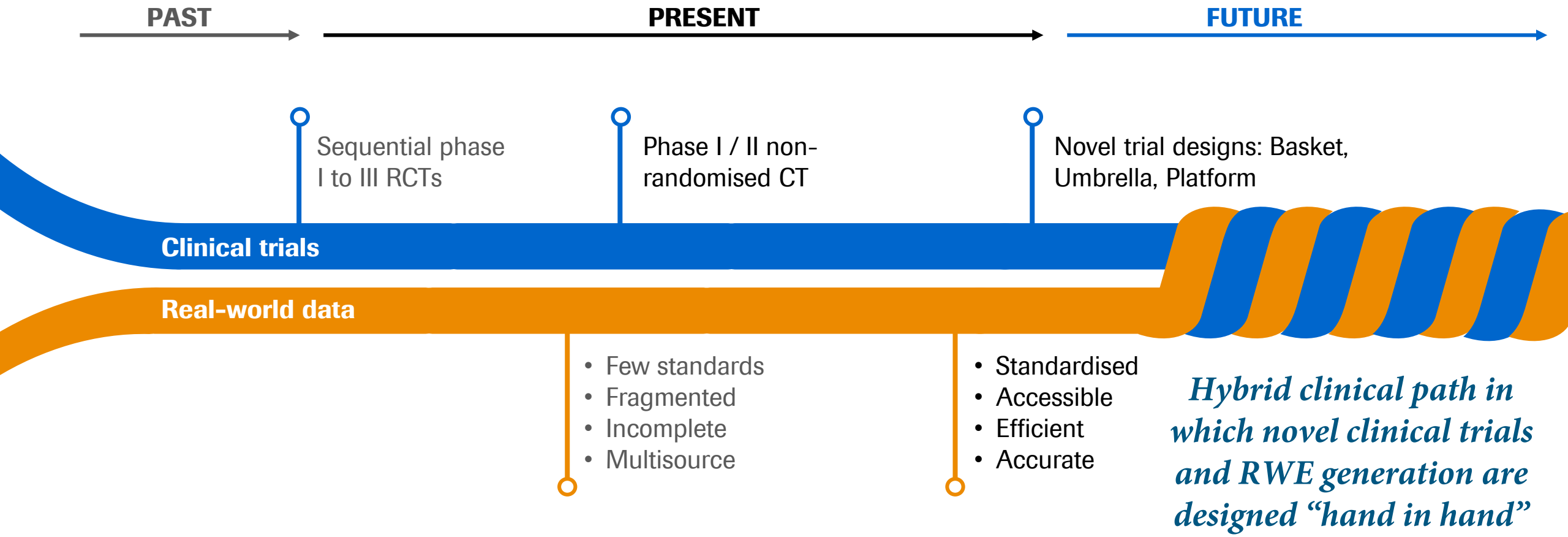
Crizotinib	2016	*ROS1* fusion lung
Rucaparib ▼	2016	*BRCA1* / *BRCA2* mut ovarian
Osimertinib ▼	2017	*EGFR*^{T790M} lung after 1st gen EGFR TKI
Brigatinib ▼	2017	*ALK* fusion lung after crizotinib
Pembrolizumab ▼	2017	MSI solid tumours (histology-agnostic)
Dabrafenib + trametinib	2017	*BRAF*^{V600E} lung
Vemurafenib	2017	*BRAF*^{V600} Erdheim Chester disease
Ivosidenib	2018	*IDH1* mut AML
Larotrectinib	2018	*NTRK1-3* fusions solid tumours (histology-agnostic)
Erdafitinib	2019	*FGFR2-3* mut / fusion bladder cancer
Entrectinib	2019	*NTRK1-3* fusions solid tumours (histology-agnostic)

* Approvals incorporating novel trial designs

AML: acute myeloid leukaemia; FDA: U.S. Food and Drug Administration; TKI: tyrosine kinase inhibitor. Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your respective local office. AstraZeneca AB: Osimertinib; Clovis Oncology UK Limited: Rucaparib; Merck Sharp & Dohme B.V: Pembrolizumab; Takeda Pharma A/S: Brigatinib.

FDA website. FDA Approved Drug Products. Available athttps://www.accessdata.fda.gov/scripts/cder/daf/ (Accessed September 2019);
Garralda, E., et al. (2019) *Mol Oncol* 13(3):549-557.

Co-evolution of clinical trials and RWD in precision medicine



CT: clinical trial; RCT: randomised controlled trial; RWD: real-world data; RWE: real-world evidence.

Opportunities and challenges for RWD use

Key considerations to harness the full potential of RWD

Collaborations

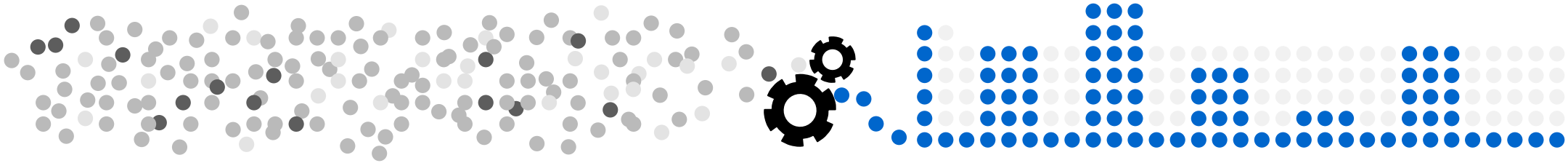
A single large initiative is more powerful than multiple initiatives with the same objective

> Set up a national / global initiative

Data protection

Data ownership, data sharing and data privacy

> Good governance structure is needed



RWD

RWE

Data considerations

RWD must be consistent, fit-for-purpose and of adequate quality to ensure generated evidence is valid[1]

> Strengthen data quality, standardisation and extraction

Methodological considerations

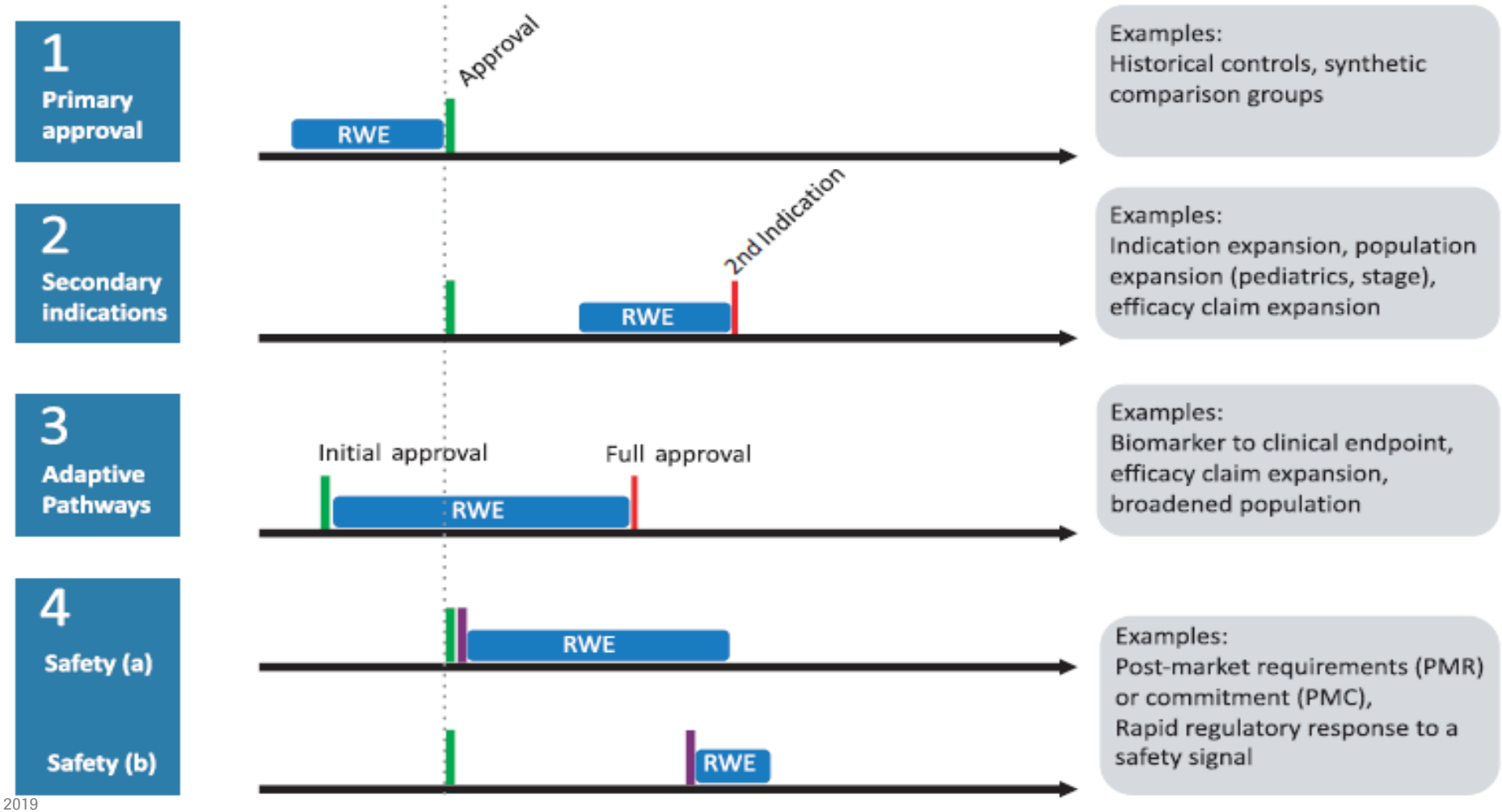
New statistical methodologies will become increasingly important and need to be validated

> Keep abreast of latest statistical analysis methods

RWD: real-world data; RWE: real-world evidence.

1. Duke-Margolis (2018) Characterizing RWD Quality and Relevancy for Regulatory Purposes; 2. Cave, A., et al. (2019) *Clin Pharmacol Ther* doi:10.1002/cpt.1426.

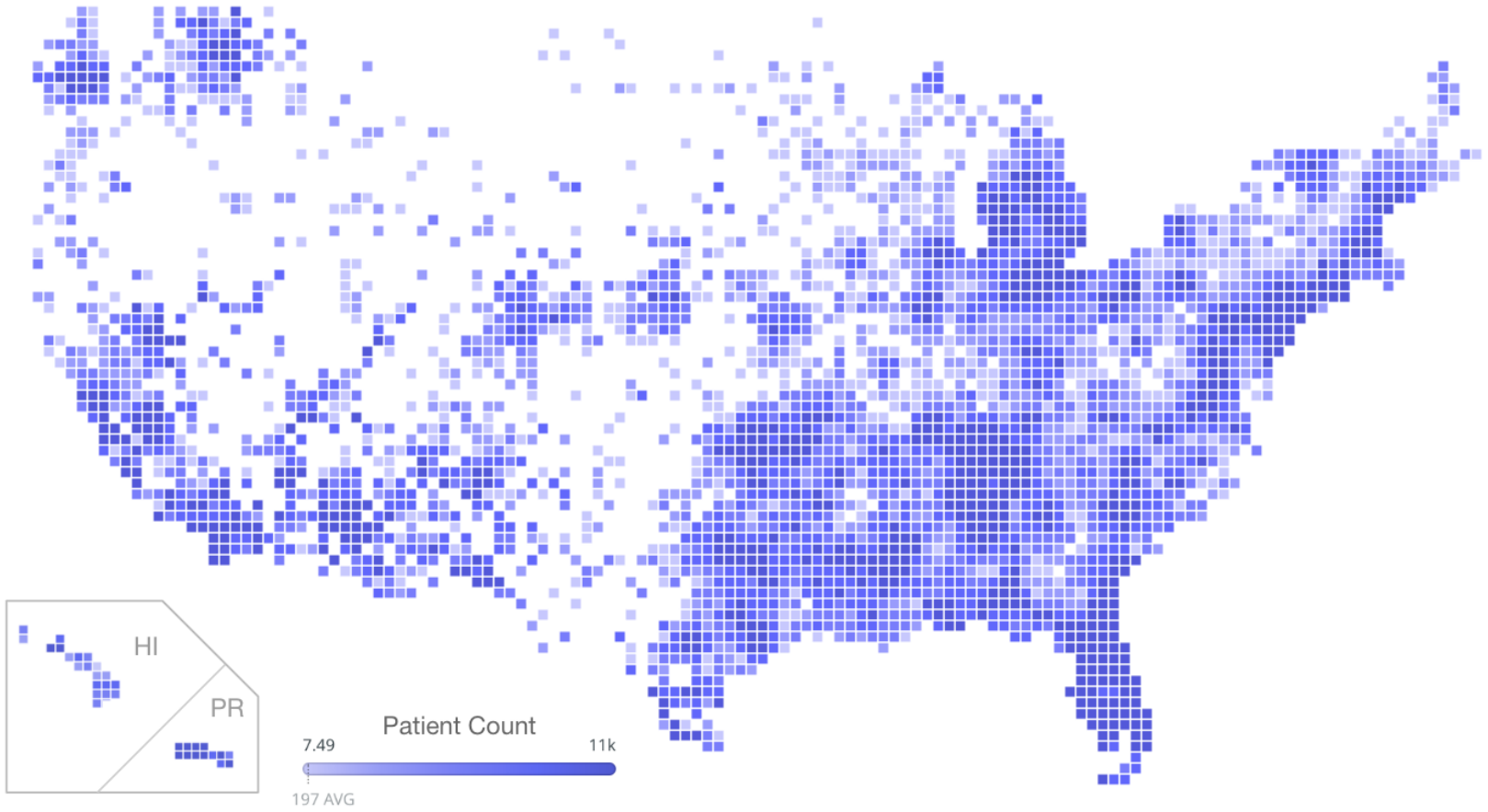
Real World Evidence in Regulatory Decision making



Franklin et al 2019

flatiron

Roche



2.2M
Active Patients

2,500
Clinicians

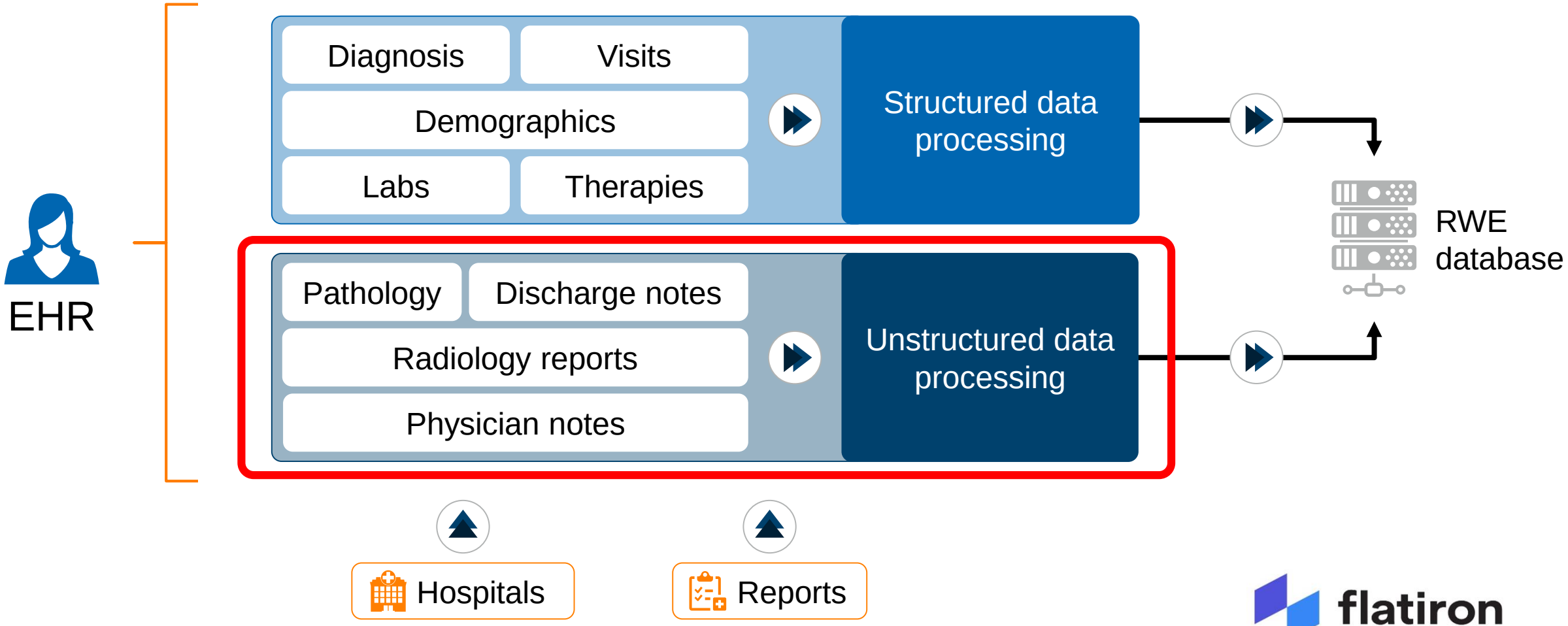
280
Cancer Clinics[1]

800
Sites of Care

* Majority are community-based clinics
1 Based on tax ID https://flatiron.com/

Flatiron: gold-standard database architecture

EHR with linkages to high value data sources



EHR: electronic health records; RWE: real-world evidence.
https://flatiron.com/

A mixture of approaches exist to abstract data

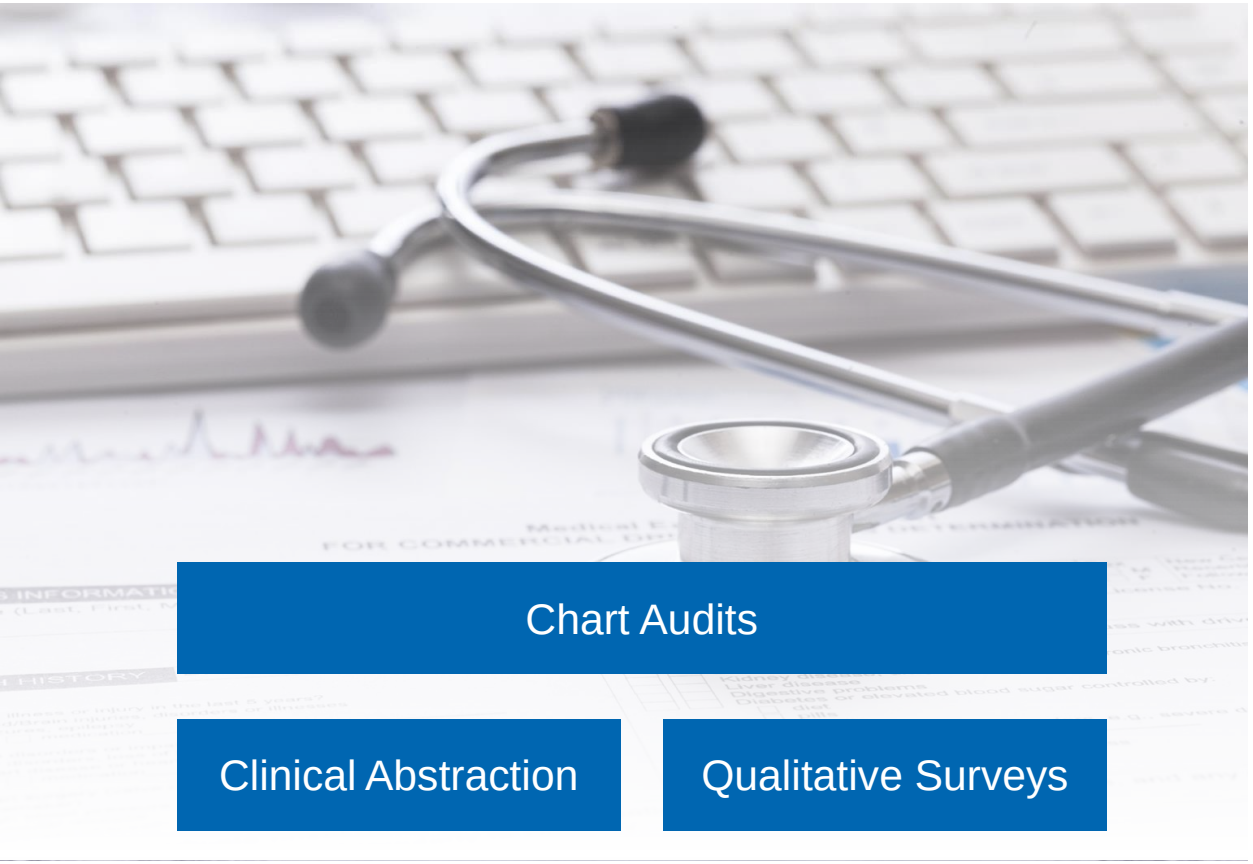


Chart Audits

Clinical Abstraction

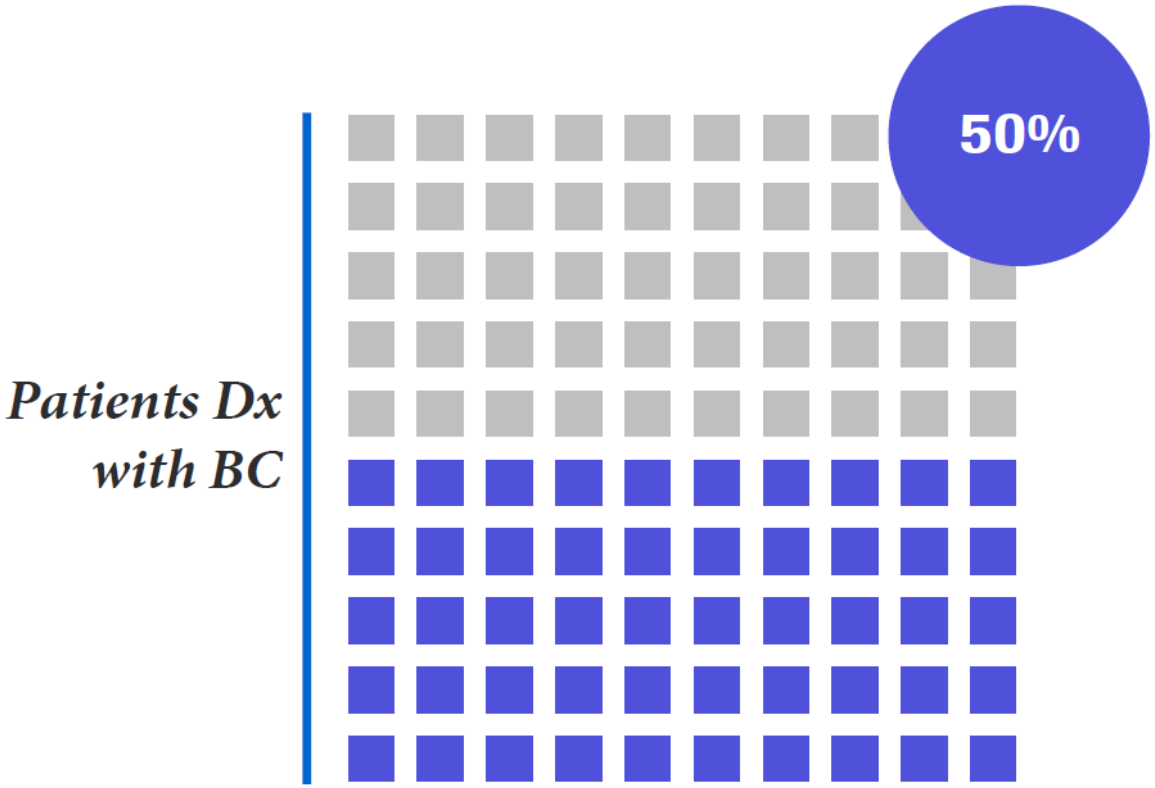
Qualitative Surveys

Machine Learning

Natural Language Processing

Artificial Intelligence

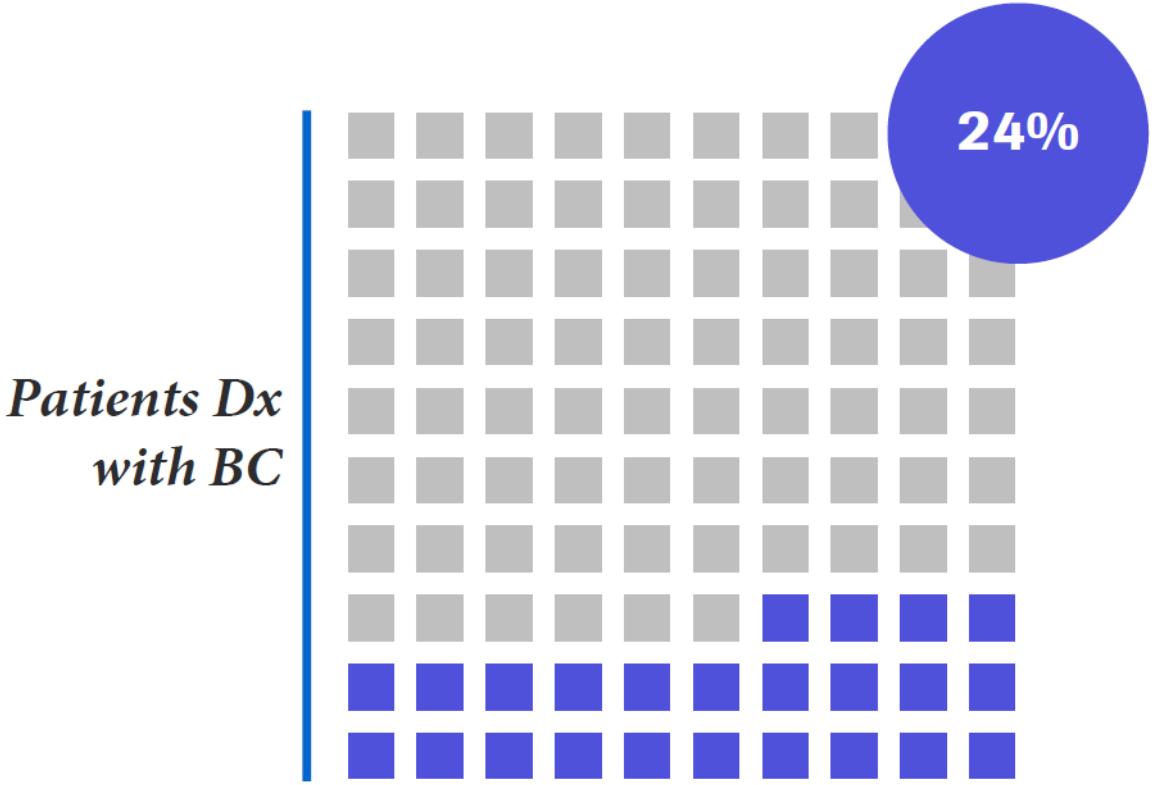
Use case: planning of a CT



- Metastatic disease
- Initiated therapy between 4/1/16 and 3/31/17
- HR + / HER2 -
- Have received drug X

Flatiron sample data. For illustrative purposes only.

Use case: planning of a CT



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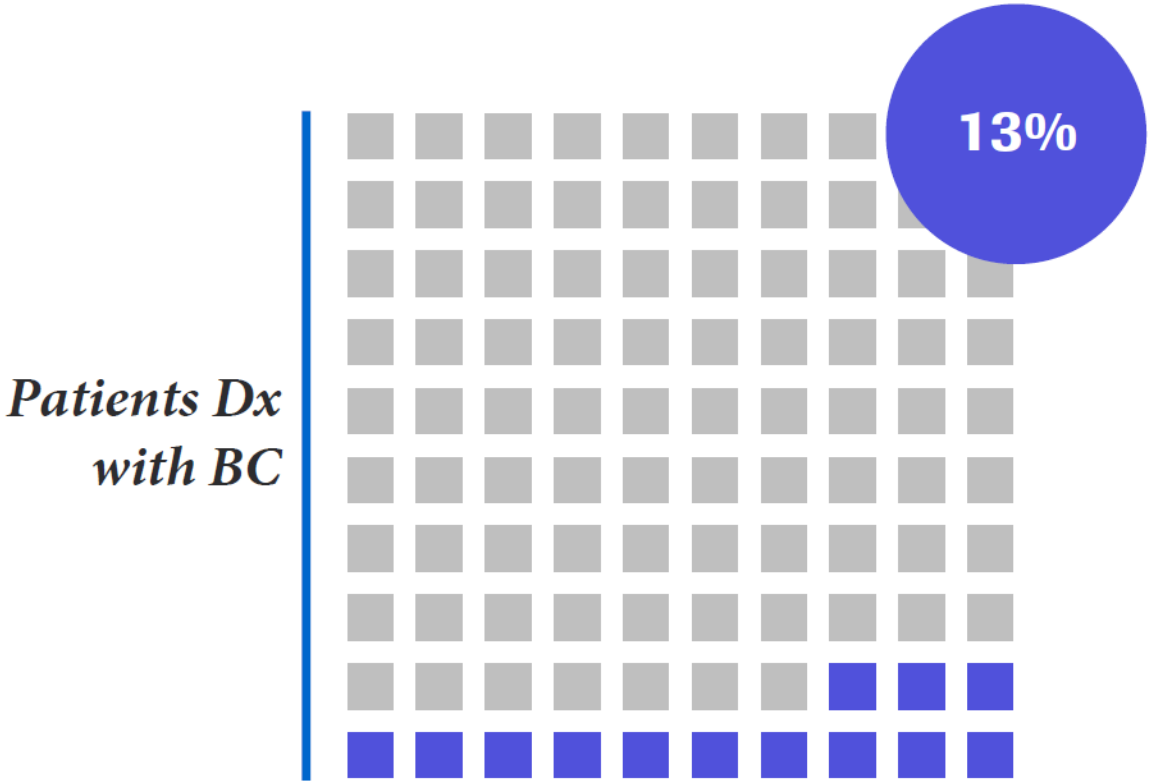

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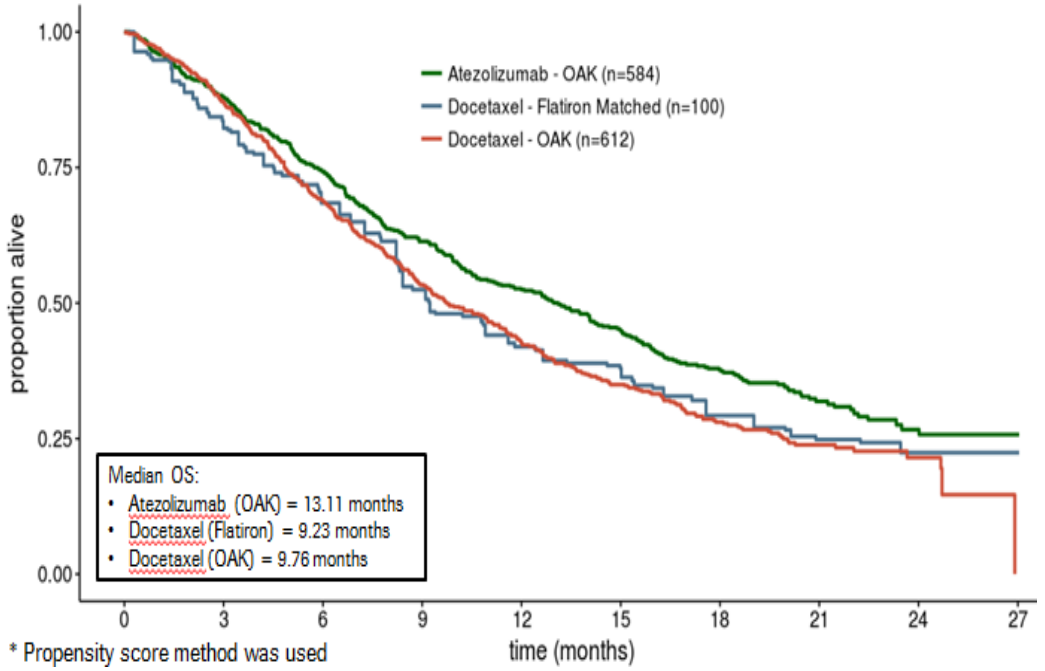
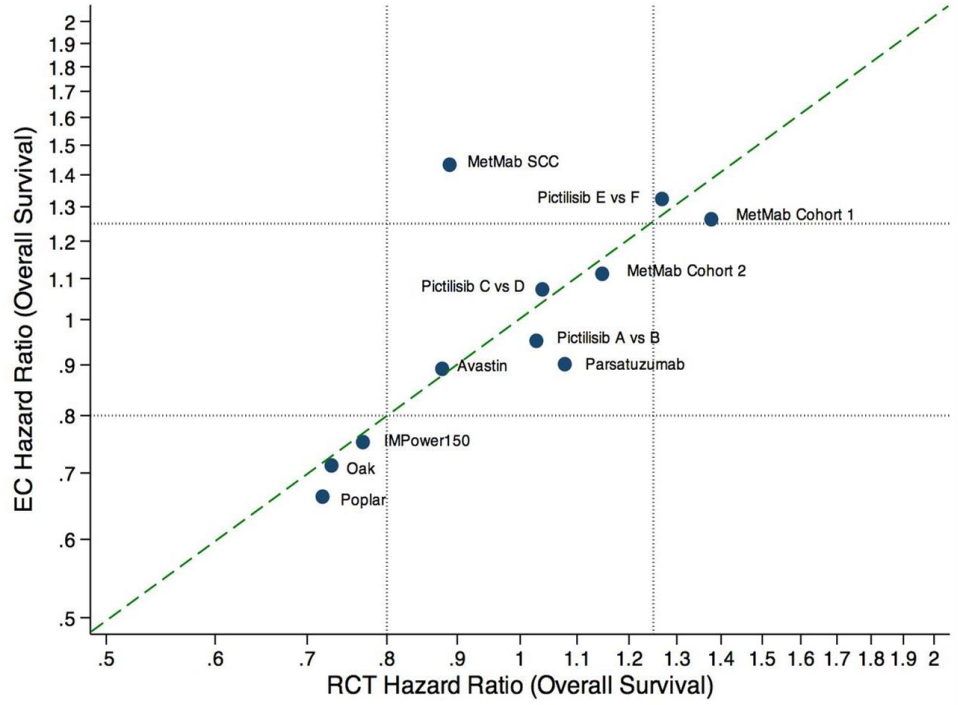
Providing confidence in RWE

Calibrating RWD to RCTs using Propensity Score Analysis

Retrospectively replicating docetaxel control arm in Atezolizumab OAK trial[1]



Replicating OS HR for nearly 11 comparisons among 8 recent NSCLC clinical trials[2]



RWE: real-world evidence; RWD: real-world data

1 Capra, W. Real World Evidence in Oncology and its Implications. American Association for Cancer Research 2018.

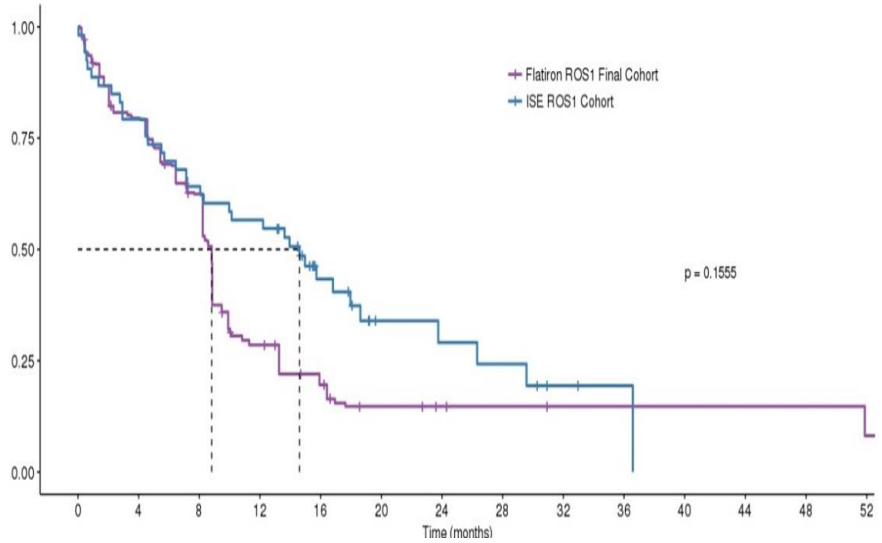
2. Carrigan G, et al., Proof-of-Concept for using External Control Arm Derived from Electronic Health Records (EHR) to Replace Control Arms from Randomized Controlled Trials (RCT). Annual Meeting of the International Society for Pharmacoepidemiology 2018.

Entrectinib ROS-1 NSCLC

Flatiron-based external control included in FDA/EMA filing

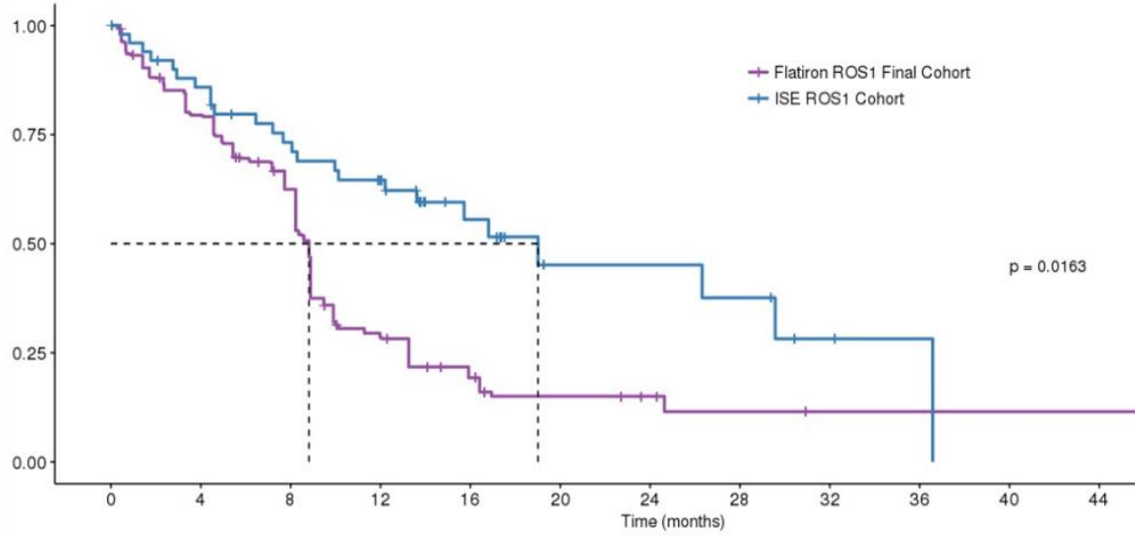
Time to treatment discontinuation:

Entrectinib (trial) vs Crizotinib (Flatiron External Control)



Progression-free survival:

Entrectinib (trial) vs Crizotinib (Flatiron External Control)



Among patients with ROS-1 advanced NSCLC, entrectinib was associated with longer time to treatment discontinuation (HR: 0.64 [95% CI: 0.4 – 1.015]) and longer progression-free survival (HR: 0.44 [95% CI: 0.26 – 0.742]) compared to crizotinib.

J Clin Oncol 37, 2019 (suppl; abstr 9070)

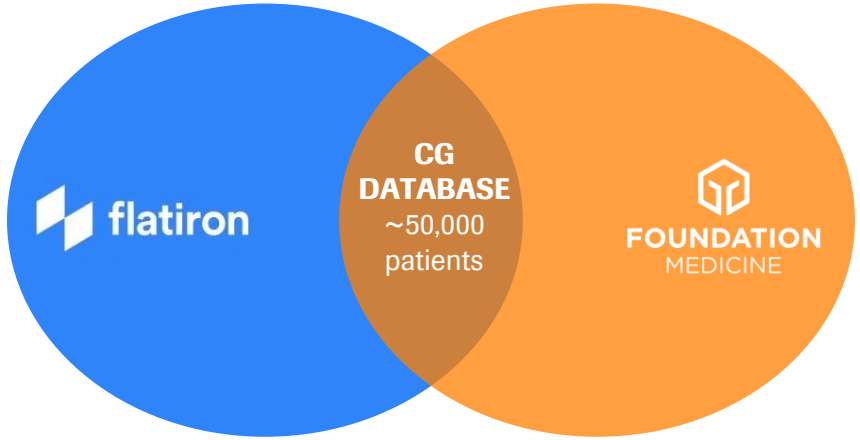
Flatiron and FMI join efforts to Combine Comprehensive Genomic data and Clinical Outcomes

flatiron

2.2M
Patients

280+
Cancer clinics

800
Unique sites of care



DATA MODEL

Enhanced clinical RWD	**Comprehensive genomic data**
Clinical outcomes	**Advanced genomic analysis**

FOUNDATION MEDICINE®

300k+
Genomic profiles

150+
Cancer subtypes

~400
Genes sequenced

2000+
Sample analysis per week

CG: clinico-genomic; FMI: Foundation Medicine, Inc.; RWD: real-world data. Flatiron 2018 from https://flatiron.com/ [Accessed June 2018]; Foundation Medicine 2018 from: https://www.foundationmedicine.com/insights-and-trials/foundation-insights#foundationcoretm; Frampton, G. M. et al. (2013) Nat Biotech 31(11): 1023-1031. [FMI information and total number of patients in CG database included is most recent as of Feb 2019.]

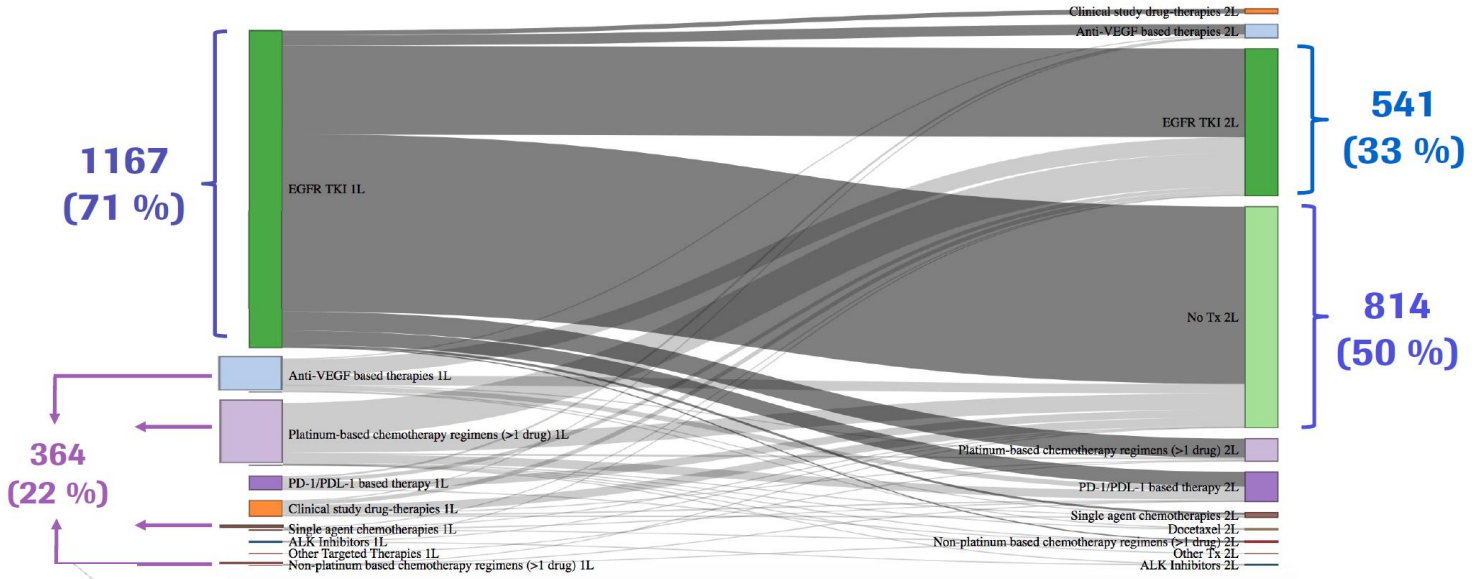
NSCLC patients

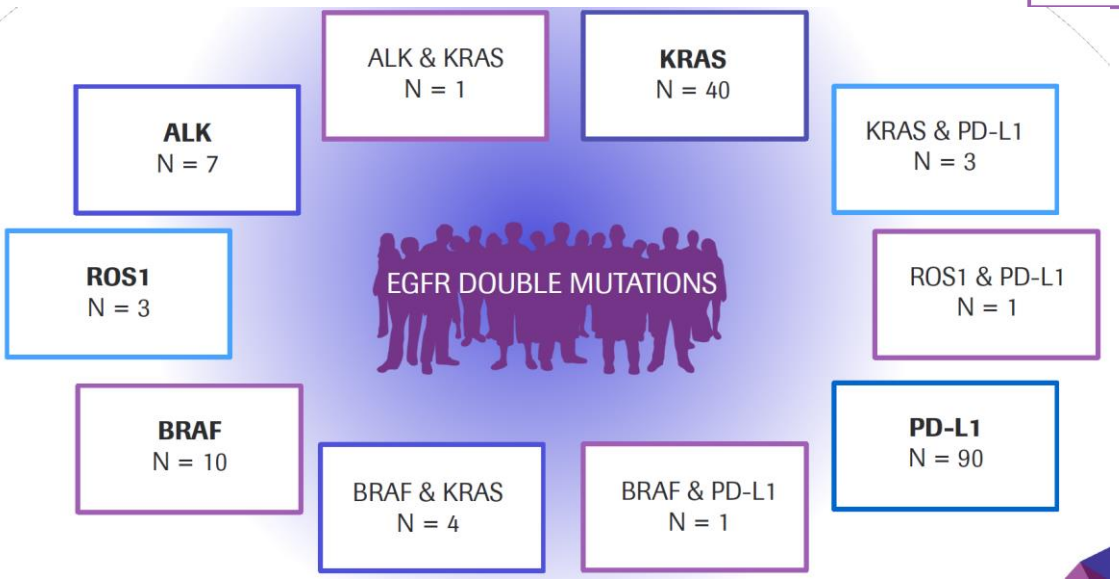
Flatiron aNSCLC data mart (N = 48,857)

1 January 2014 – 31 May 2018 (N = 31,532)

Non-squamous NSCLC histology (N = 23,519)

Positive EGFR test result date on or after their NSCLC diagnosis and prior 2L initiation (N = 1,645)





>20% der Patienten erhielten keinen EGFR TKI in der 1. Linie
50% der Patienten erhielten keine 2. Linien-Therapie
160 Patienten hatten zumindest eine weitere Mutation oder waren PD-L1 pos.

Roche, Data on file

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Challenging for physicians and authorities to remain up-to-date with the scientific knowledge[10]

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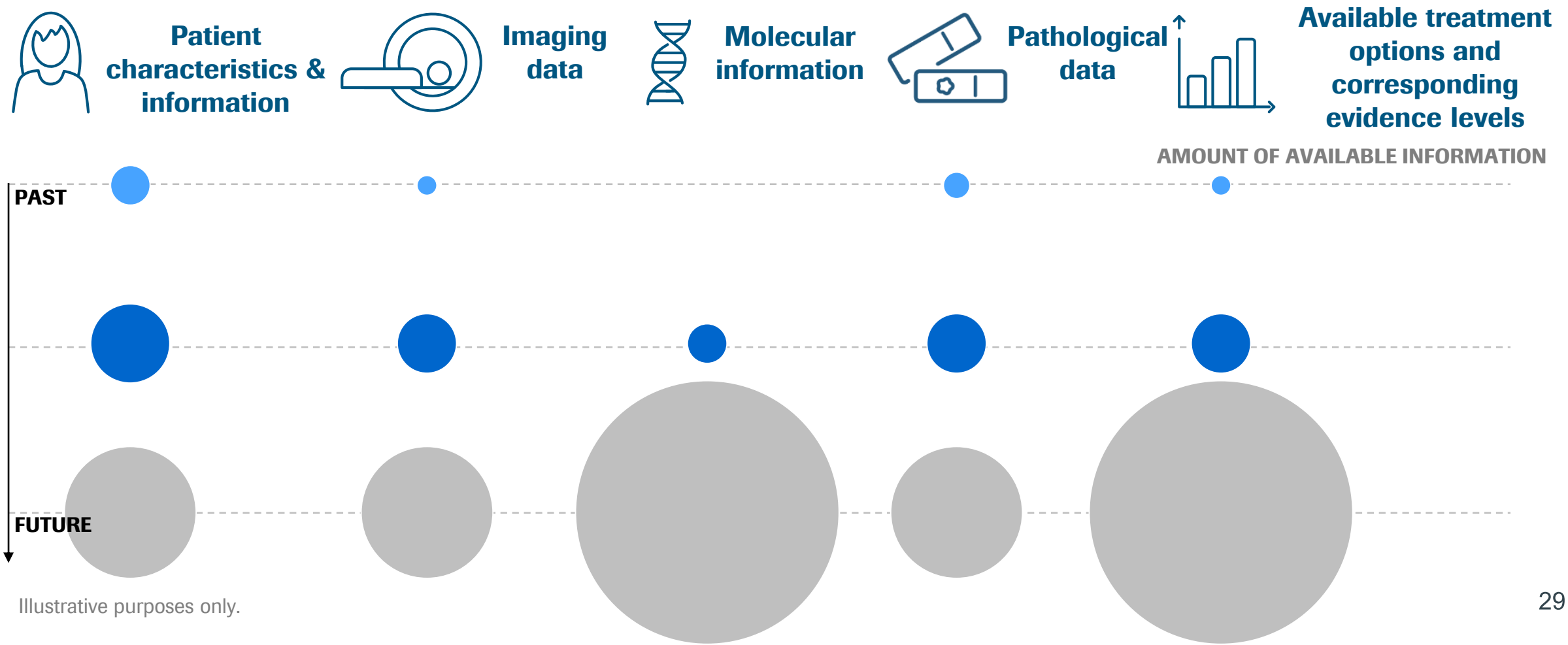
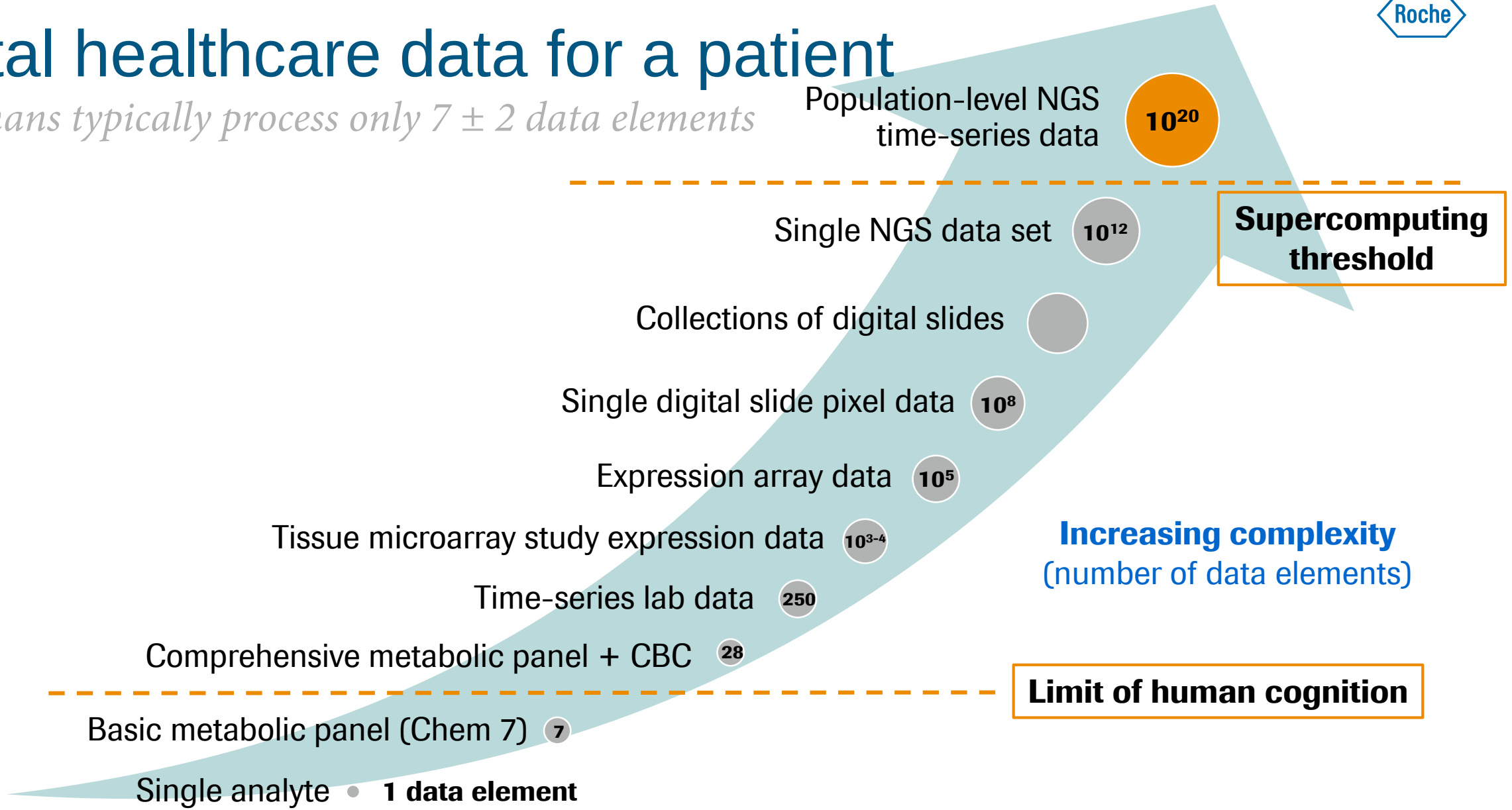
The ever-increasing amount of information complicates decision making



Illustrative purposes only.

Total healthcare data for a patient

Humans typically process only 7 ± 2 data elements



CBC: complete blood count; NGS: next-generation sequencing.
Figure modified and presented with permission of Dr Ulysses Balis, Michigan Medicine, Ann Arbor, Michigan.

AI will disrupt healthcare

Countless opportunities exist within all areas of medicine

Currently and in the future, AI can …

Disease prevention	› Predict population health patterns, chronic disease incidence
Diagnosis	› Improve diagnostic accuracy, reduce diagnostic TAT › Enhance clinical decision support tools in the EHR
Treatment	› Assist physicians design treatment plans and monitor patient response to therapy (truly personalised medicine) › Enhance robotic surgery and other procedures
Patient management	› Improve multi-disciplinary conferences / tumour boards, predict disease recurrence › Reduce patient length of stay and hospital readmission rates
Research	› Discover new relationships, combine data in new ways and improve the quality of translational and basic science research

AI: artificial intelligence; EHR: electronic health record; TAT: turnaround time.
Source: Dr McClintock's experiences in Clinical Informatics practice and Medical Futurist (2019).
Available at https://medicalfuturist.com/top-artificial-intelligence-companies-in-healthcare (Accessed September 2019).

How will AI assist healthcare providers in the near future?

Image classification and diagnosis[1,2]

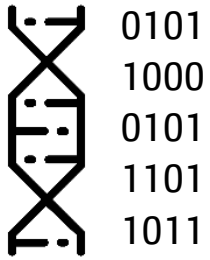
Examples:

- Skin cancer detection
- Diabetic retinopathy

Benefits:

- **Reduced time to diagnosis**
- Can enhance skill of physician to improve accuracy

Analysis of large datasets[1,3]



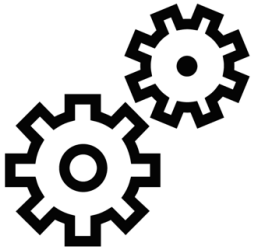
Examples:

- Genomic data
- Real-world data

Benefits:

- **Rapid identification of novel patterns**
- Generation of novel hypotheses

Automation of repetitive tasks[4]



Examples:

- Automated note taking
- Prioritisation of patient visits

Benefits:

- More detailed health records
- **More time to spend with patients**

1. Londhe V. and Bhasin, B. (2019) *Drug Discov Today* 24:228-32; 2. Available at: http://www.healthtechzone.com/topics/healthcare/articles/2016/12/05/427750-why-ai-important-the-future-medicine.htm (Accessed September 2019); 3. Available at: https://medicalfuturist.com/top-artificial-intelligence-companies-in-healthcare/ https://medicalxpress.com/news/2019-08-deep-ai-atrial-fibrillation-rhythm.html (Accessed September 2019);
4. Available at: https://www.healthcareitnews.com/news/ai-powered-voice-note-taking-saves-orthoatlanta-hour-physician-day (Accessed September 2019).

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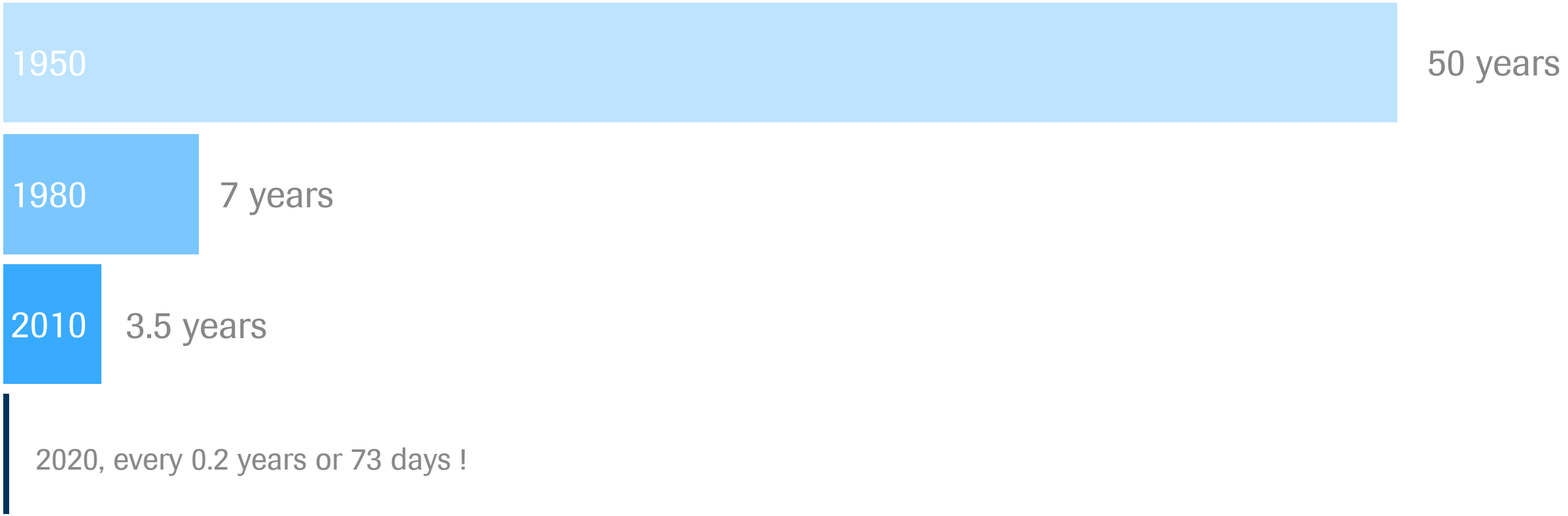
Medical knowledge doubling time



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3116346/

Emerging classifications aim to aid in clinical decision-making

ESCAT target classifications[1,2]

Tier I	Targets ready for implementation in routine clinical decisions
Tier II	Investigational targets likely to define patients who benefit from a targeted drug, but additional data needed
Tier III	Clinical benefit previously demonstrated in other tumour type or similar molecular targets
Tier IV	Pre-clinical evidence of actionability
Tier V	Evidence supporting co-targeting approaches
Tier X	Lack of evidence for actionability

OncoKB classification for actionable mutations[3]

Level 1	Alterations that are FDA-approved biomarkers for particular drugs for a certain indication
Level 2	Alterations that are FDA-approved biomarkers for particular drugs in another indication
Level 3	Alterations for which clinical evidence exists to link the alteration to a drug response for another indication
Level 4	Alterations for which preclinical evidence exists to link the alteration to a drug response

ESCAT: ESMO scale for clinical actionability of molecular targets; ESMO: European Society for Medical Oncology; FDA: U.S. Food and Drug Administration.

1. Mateo, J., et al (2018) *Ann Oncol* 29:1895-902; 2. ESMO Press Release. Available at https://www.esmo.org/Press-Office/Press-Releases/ESCAT-scale-DNA-actionability-molecular-targets-Mateo-Andre (Accessed September 2019); 3. Varghese, A.M., et al. (2017) *Ann Oncol* 28: 3015–21.

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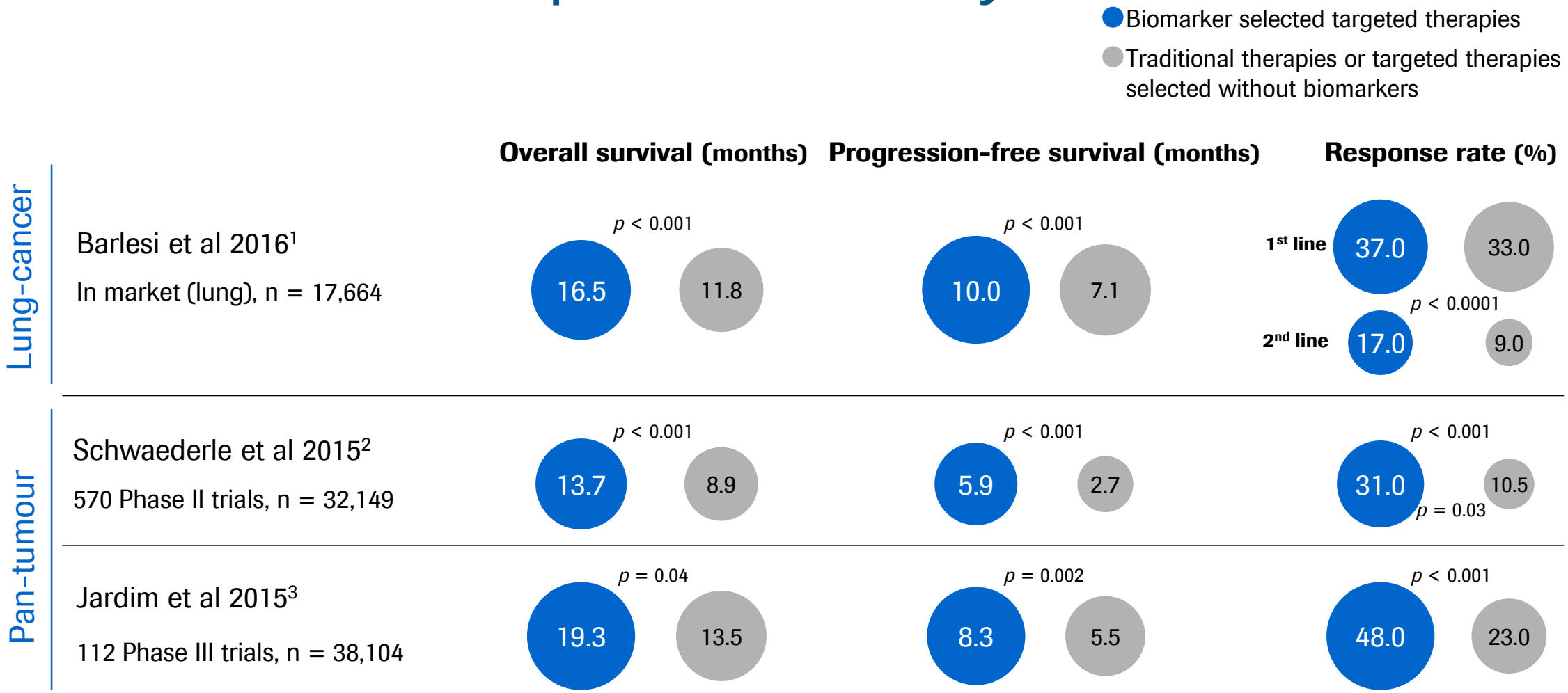
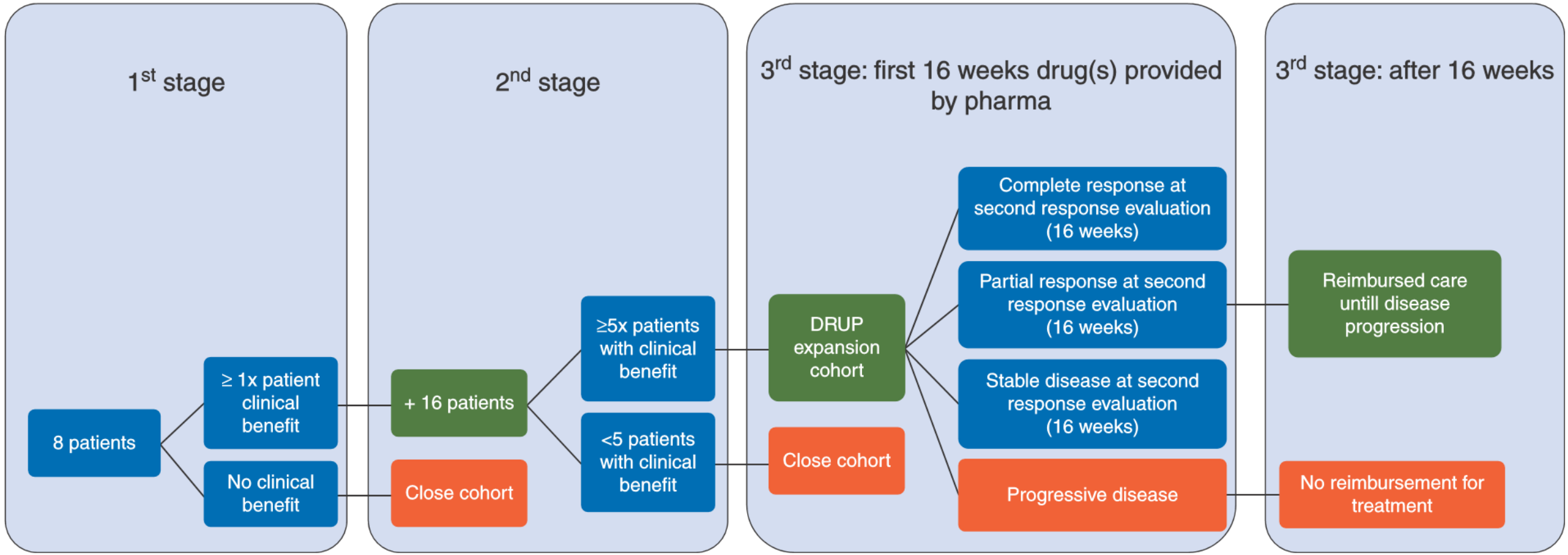
Biomarker-based approaches are associated with improved efficacy



1. Barlesi, F., et al. (2016) *Lancet* 87:1415-26; 2. Schwaederle, M., et al. (2015) *JCO* 33:3817-25; 3. Jardim, D.L., et al. (2015) *J Natl Cancer Inst* 107.

Reimbursement - a risk-sharing approach for treatment of cancer patients



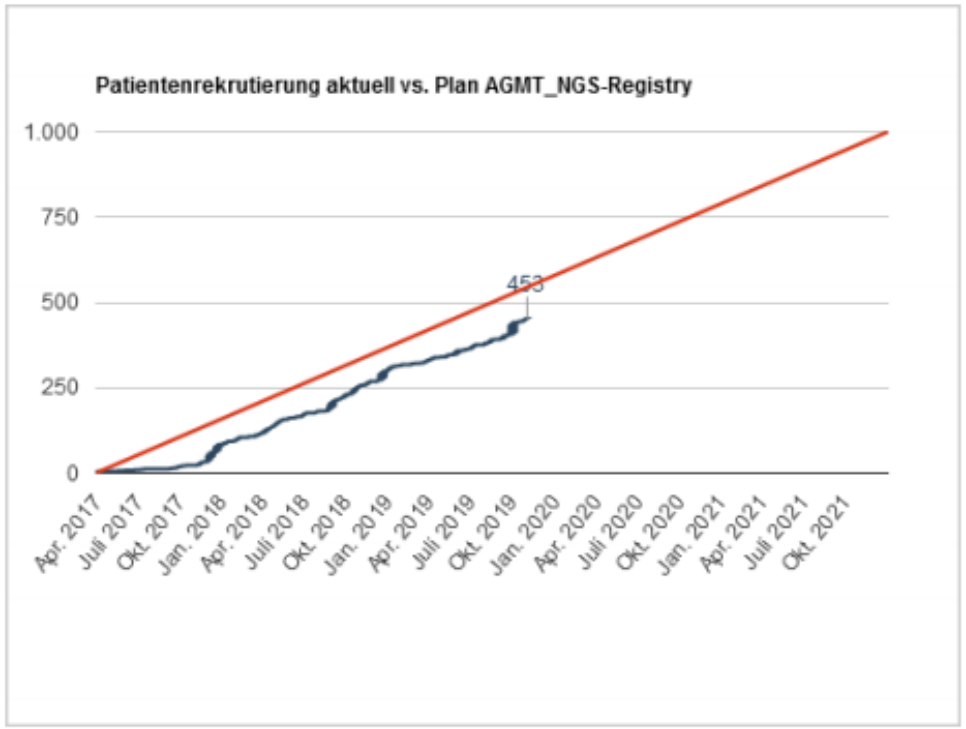
an Waalwijk van Doorn-Khosrovani SB. Ann Oncol. 2019 May 1;30(5):663-665.

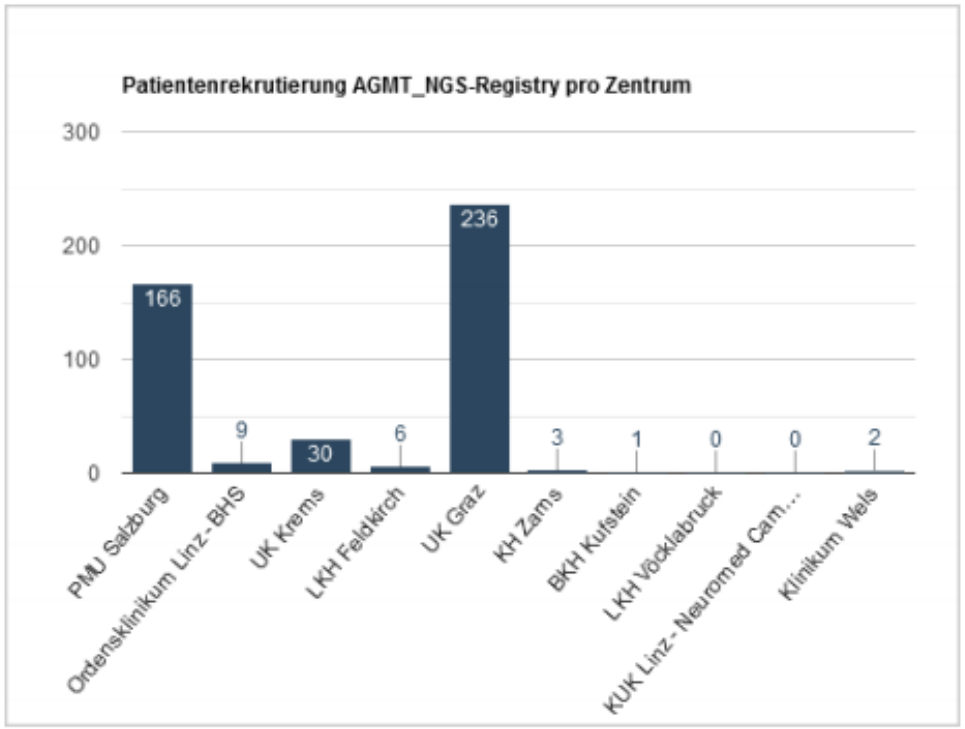
NGS Register - Austria

AGMT
Austrian Group • Medical • Tumor Therapy

AGMT
Newsletter Oktober 2019

AGMT Jahresmeeting 2019
15. – 16. November 2019





Standing Committee Oncology

Task Force: Personalized Healthcare

PHARMIG
Verband der pharmazeutischen Industrie Österreichs

Roche

Goal

Create a „Position paper“ for personalized healthcare (in oncology)

- What is personalized Healthcare
- National Actionplan for PHC
- New/innovative pricing/funding solutions
- Real World Data e.g. registries
- Need for high quality diagnostics

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Doing now what patients need next