Vintura Life Sciences Event
Amsterdam, 28 November 2014

Challenges and opportunities to implement personalized medicine

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Applications of Personal Genomes in Clinical Care

From Cradle to Grave

Birth planning
- Screening carriership

Disease prevention
- BRCA, CFTR

Aging
- Understanding healthy aging

Pregnancy
- NIPT (trisomy 13/18/21, gender, carriership)

Cancer (Oncology)
- Personalized treatment

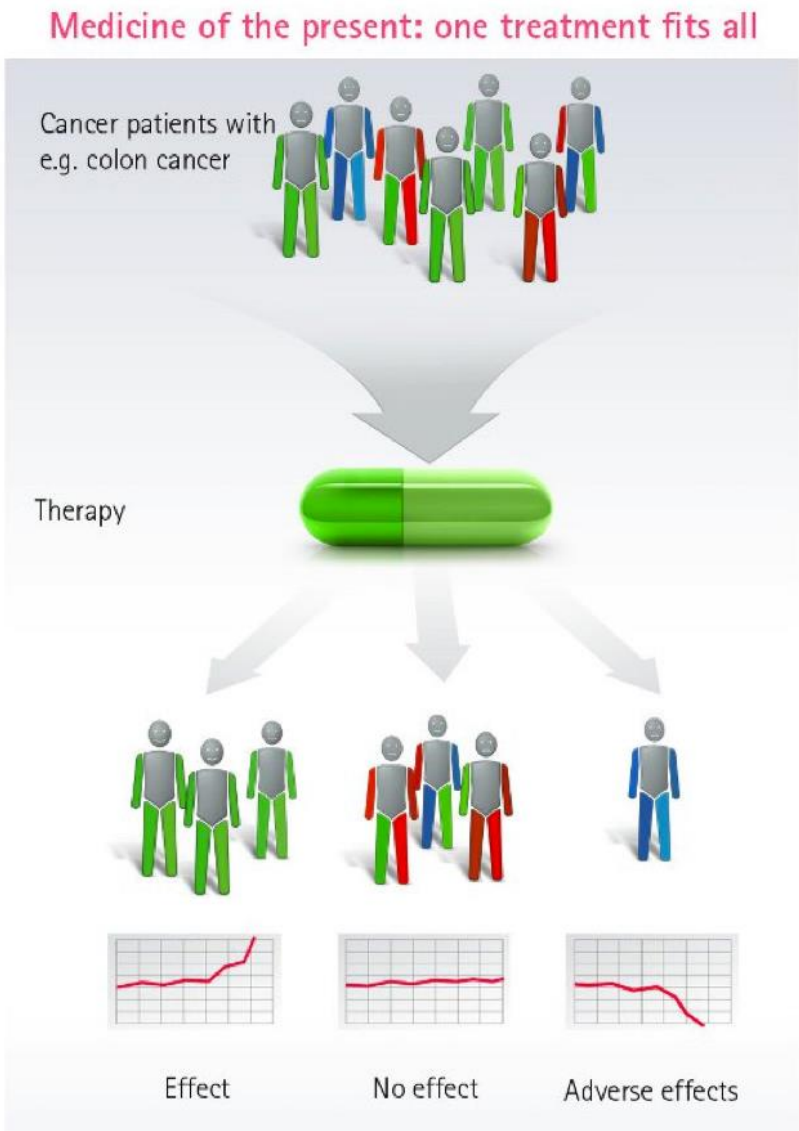
Newborn
- Replacing heel prick: detection rare congenital disease

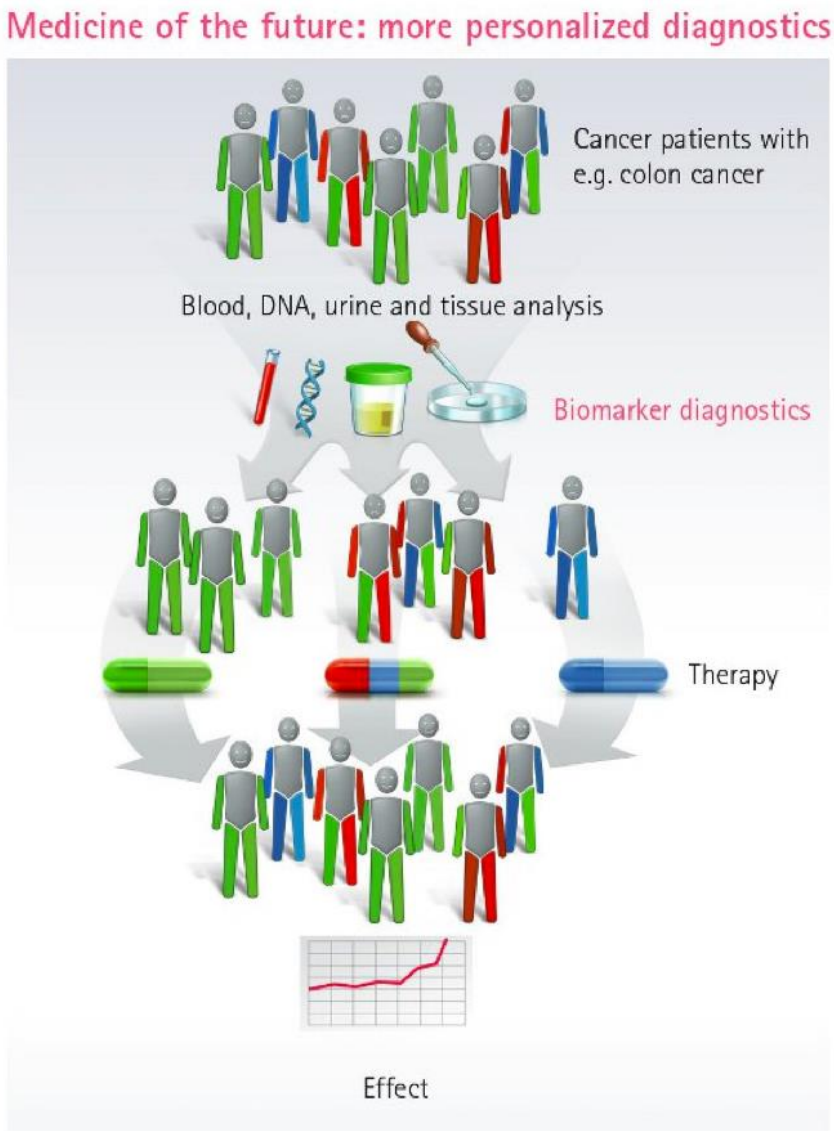
Pharmacogenetics
-drug/dose choice

Death
- Genetic autopsy unexplained disease cause

Diagnostics congenital disease (Clinical Genetics)
- **De novo mutation screening**
- **Whole genome scan**

The Opportunity: Personalized Cancer Treatment

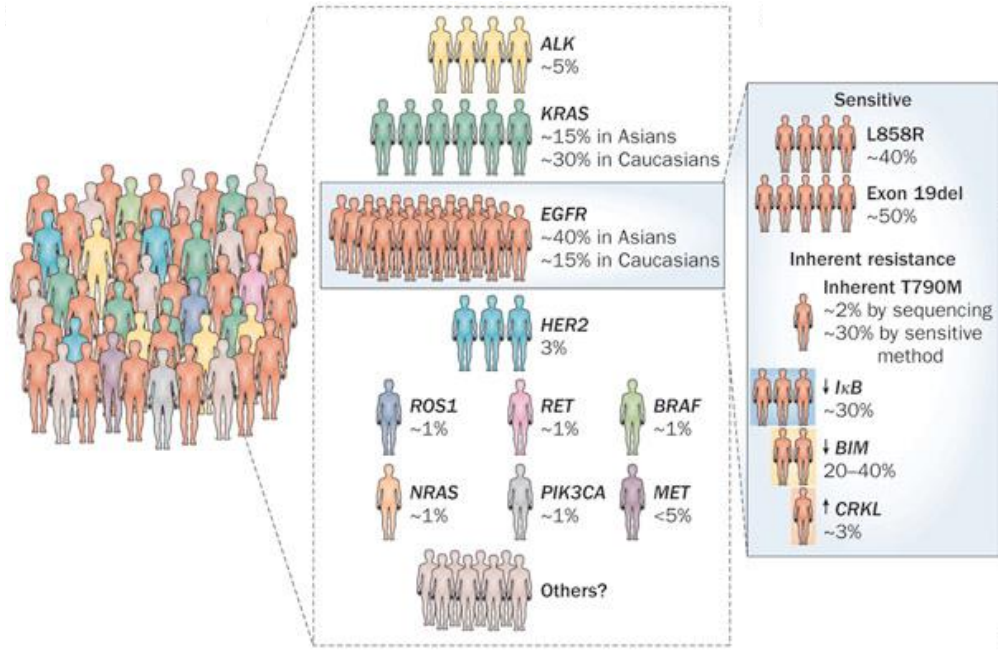




Personalized Cancer Treatment: The dilemma

Every patient is unique

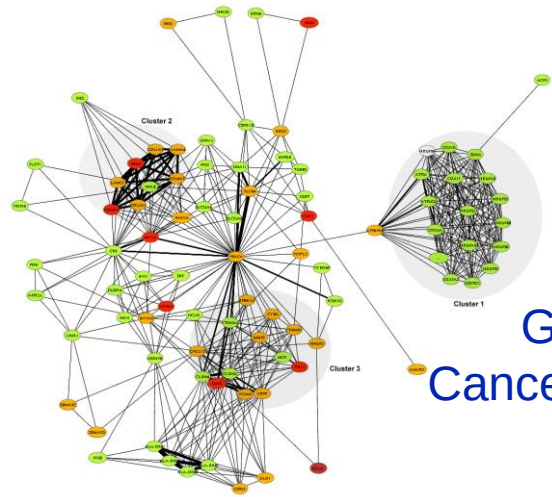
Mutated genes and combinations



How to learn from retrospective cohorts?

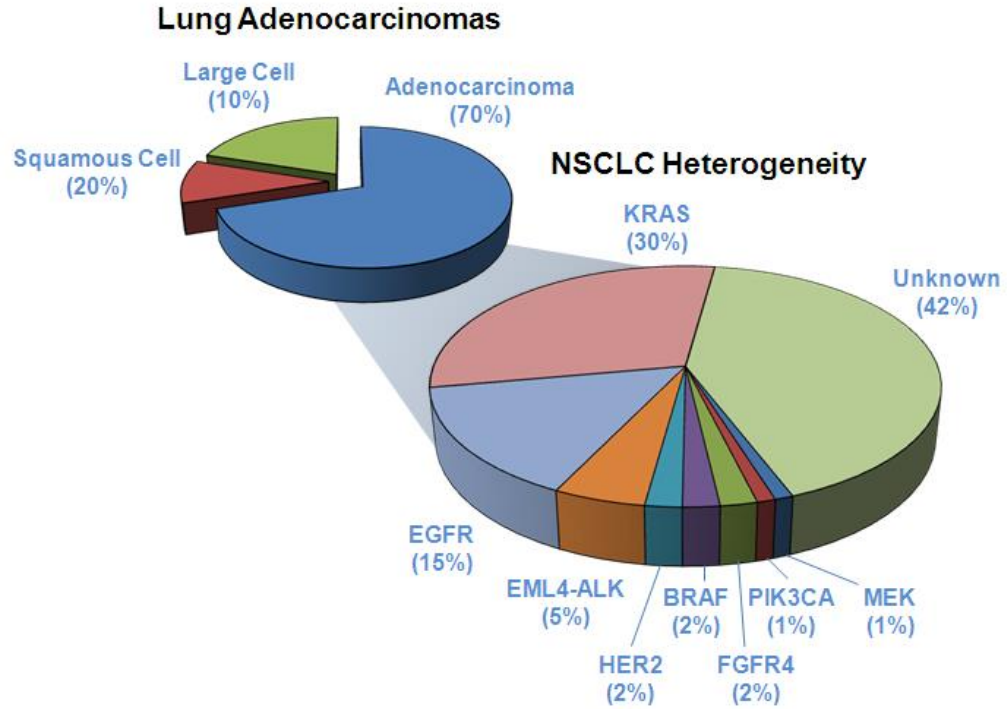
Create experimental groups with common genetic aberrations

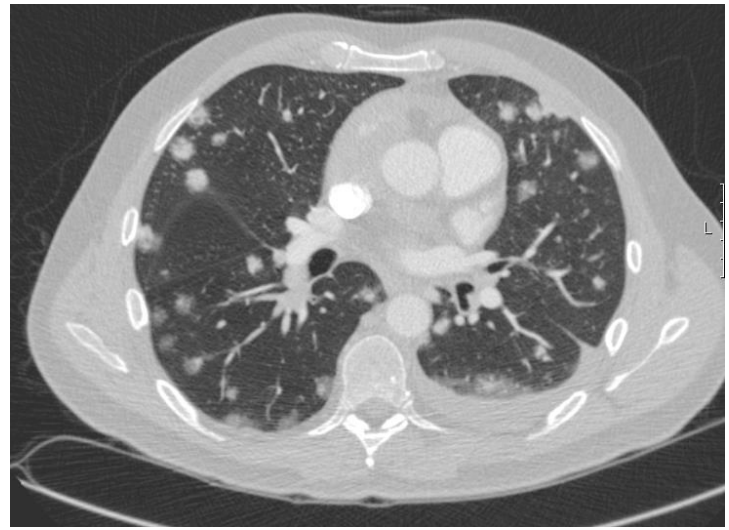
Groups quickly become small, especially in combination with available treatments: large experimental cohorts required!

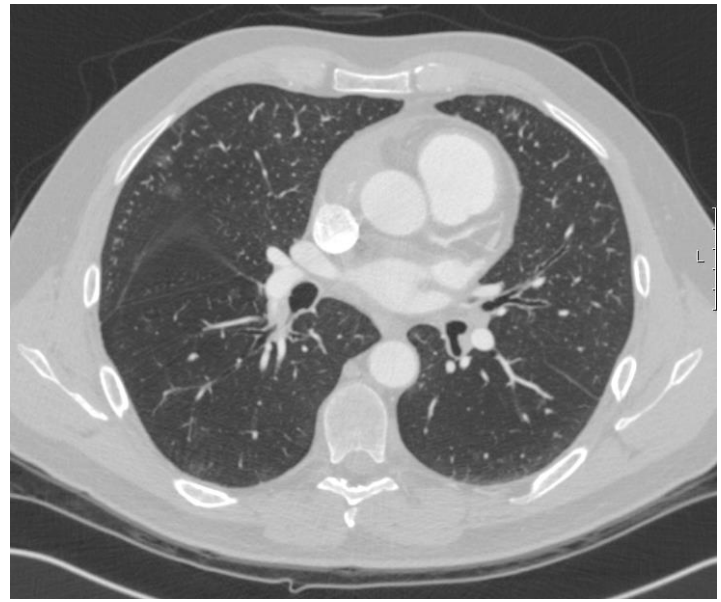


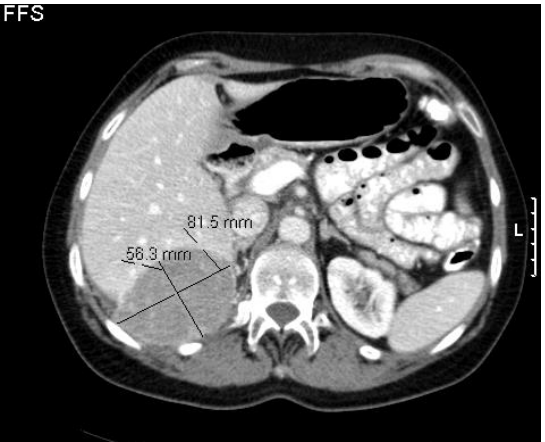
Gene networks
Cancer systems biology

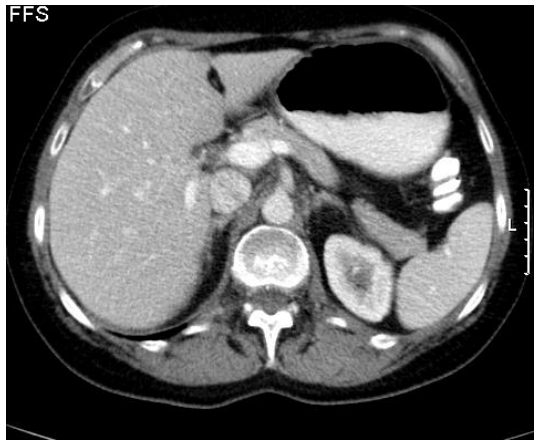
Enriching for genetic changes that confer sensitivity to treatment











Making progress in personalized medicine

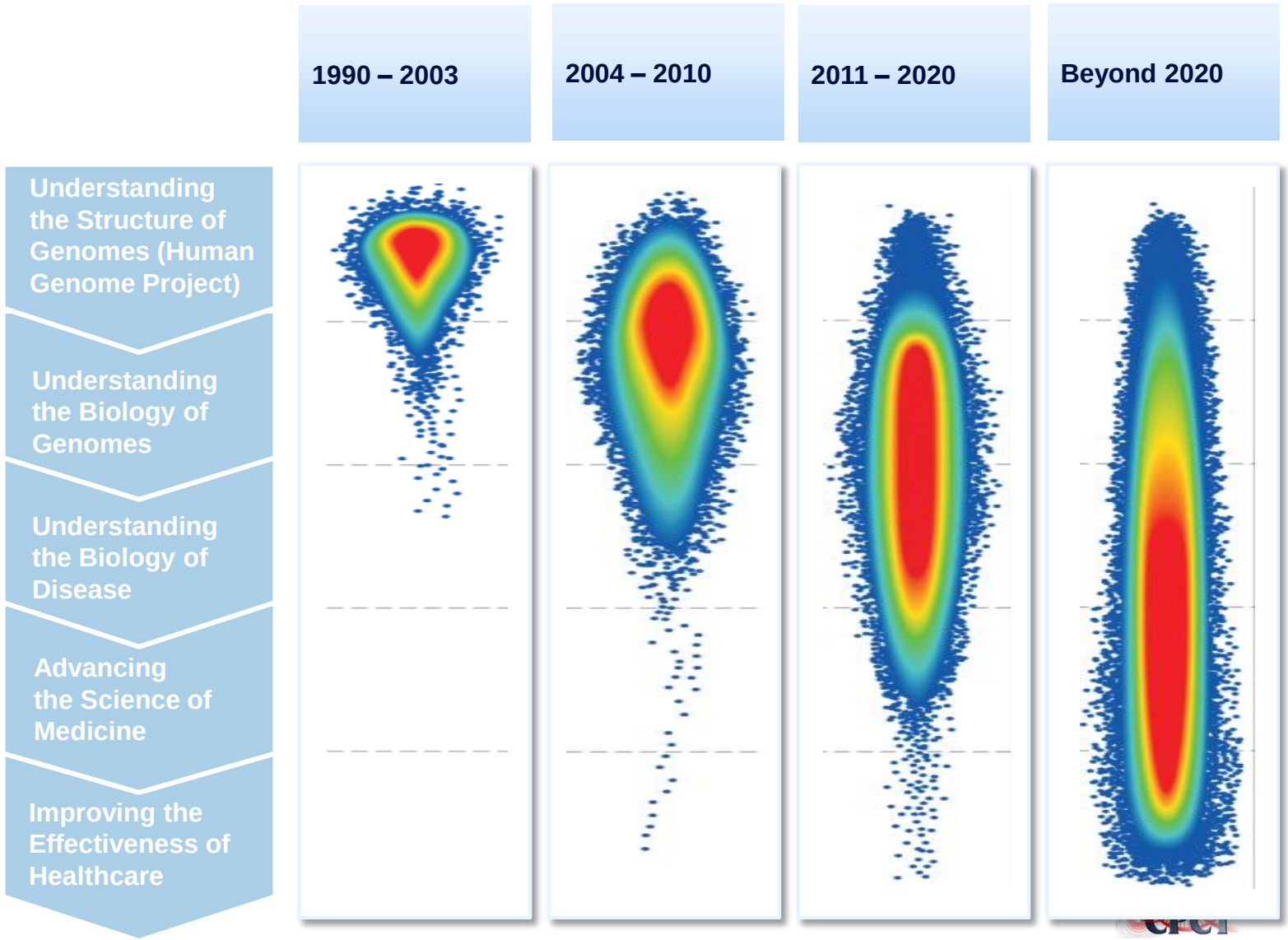
Mutational and/or expression profiling of tumors have greatly improved patient selection for treatment and reformed our thinking about cancer

- Vemurafenib, trastuzumab, imatinib, crizotinib, and many more

Current limitations of this approach

- Subdivision in increasingly smaller groups
- Response rates generally lower than anticipated
- Development of resistance

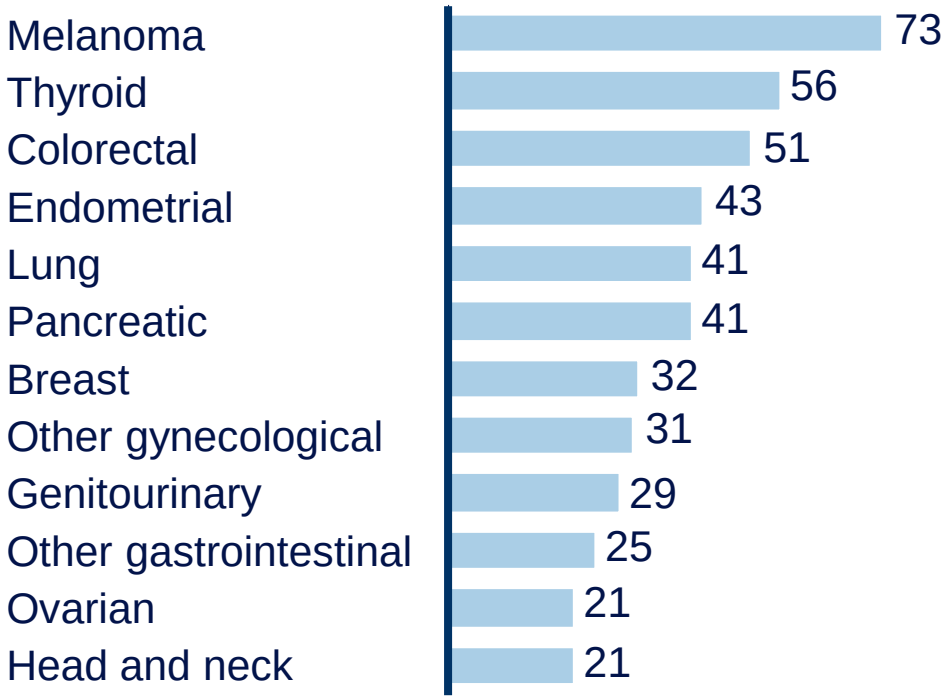
It takes research, time and investments to start realizing the promise of personalized care



We have increasing understanding of disease heterogeneity

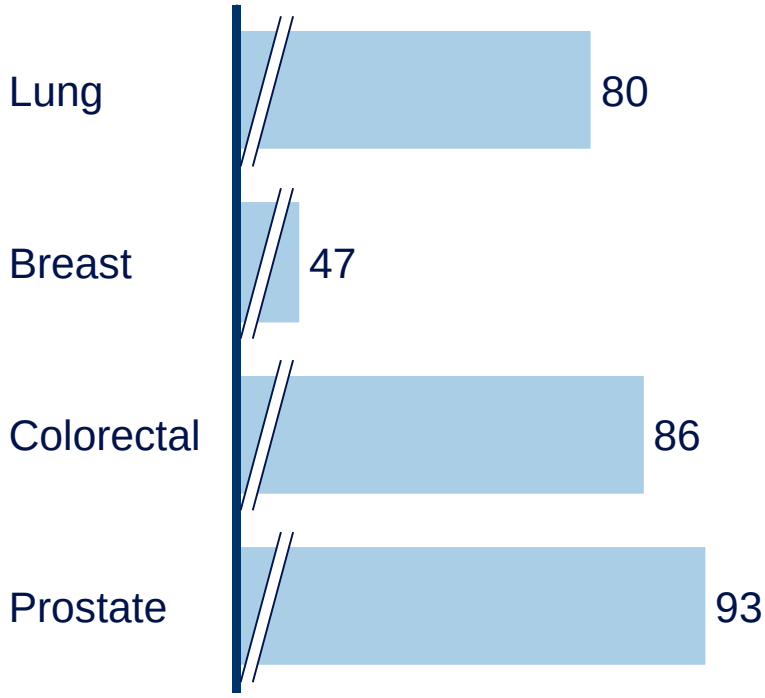
Type of cancers driven by known genetic mutations

Percent of total patients



Hypermutated genes identified by Cancer Genome Atlas

Number of genes[1]



We are also beginning to better understand heterogeneity in other disease areas including immune-related and transplant

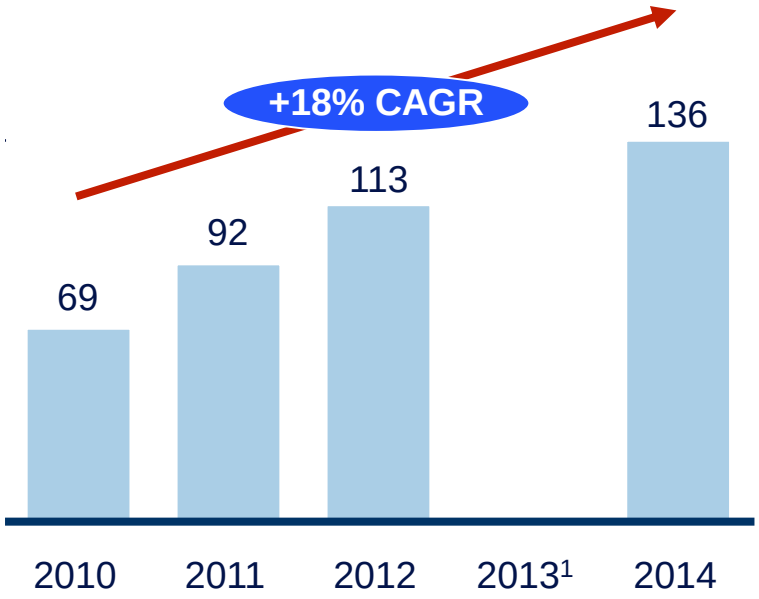
1 Based on q-value analysis using MutSig software from the Broad Institute

SOURCE: Wall Street Journal, 2011, Personalized Medicine The Path forward

Over the past few years in the US, number of drugs and biomarkers referenced by FDA has steadily increased

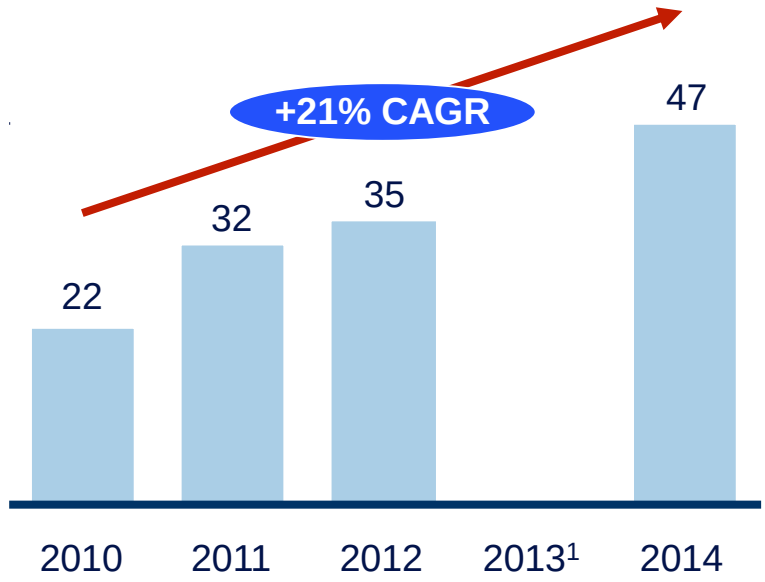
FDA-approved drugs associated with a biomarker

Number of FDA-approved drugs with pharmacogenomic information in label



Distinct biomarkers referenced

Number of biomarkers referenced in labels of FDA-approved drugs

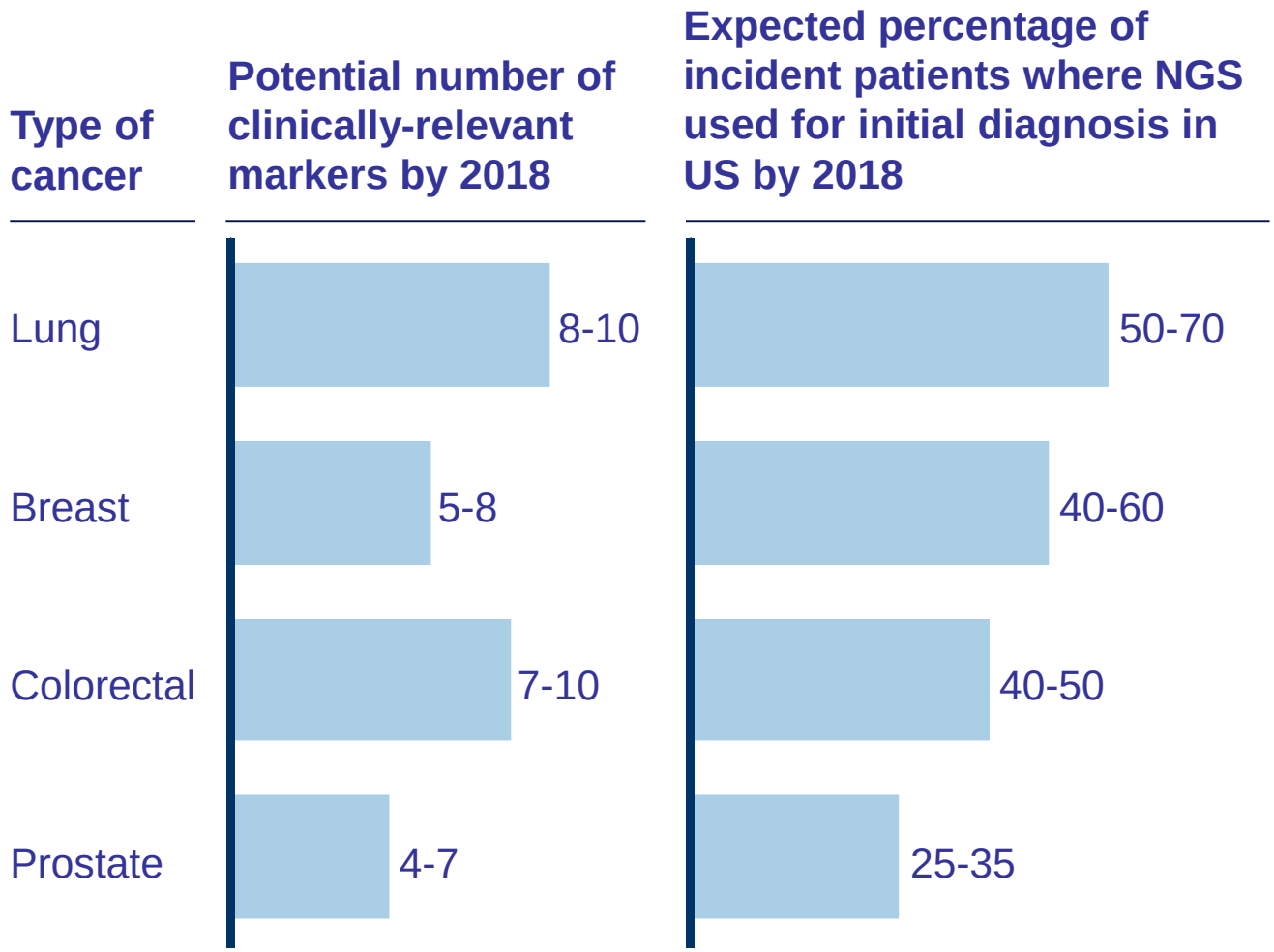


Oncology used to be the dominant therapeutic area for drugs mentioning biomarkers, but more drugs in other therapeutic areas, including psychiatry (25), infectious diseases (16), and neurology (10), mention biomarkers in their labels

1 Data not available

SOURCE: FDA Table of Pharmacogenomic Biomarkers in Drug Labeling, McKinsey analysis

Significant penetration of next generation sequencing in oncology expected in the future



SOURCE: Expert interviews

D Until now Payors were hesitant to adopt personalized medicine in spite of these potential benefits, but start to rapidly change

63% … of Payors believe that Personalized medicine is going to increase cost of healthcare in the next 3-4 years

81% … of Payors cited the lack of high quality data and the evidence base as the biggest barrier in adoption of Personalized medicine

70% … of Payors do not reimburse for next generation sequencing in oncology today, but this is rapidly changing

74% … of Payors are exploring pathways for therapy selection based on genomic information

> “Reimbursement models will need to change to keep up with the pace of change of personalized medicine”

SOURCE: Payor survey US

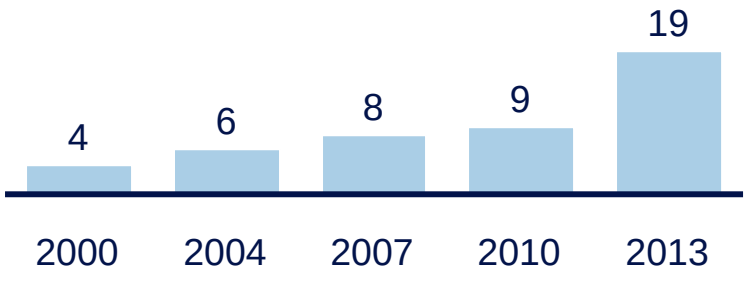
Contents

- Worldwide Personalized medicine in oncology is expected to deliver significant value and will revolutionize the way patients are treated
- **Adopting the new technologies of next generation sequencing will bring significant value for payors**
- CPCT is very well positioned to fulfill the need for a national sequencing center in the future
- For successful implementation, key criteria have to be met to realize a national sequencing center

There is value to be captured through personalized medicine

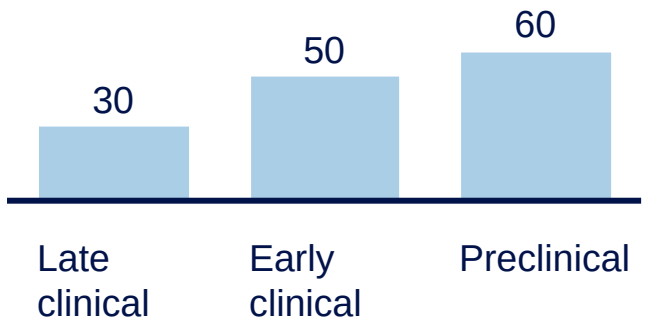
Number of FDA-approved Companion Diagnostics

Total number of products



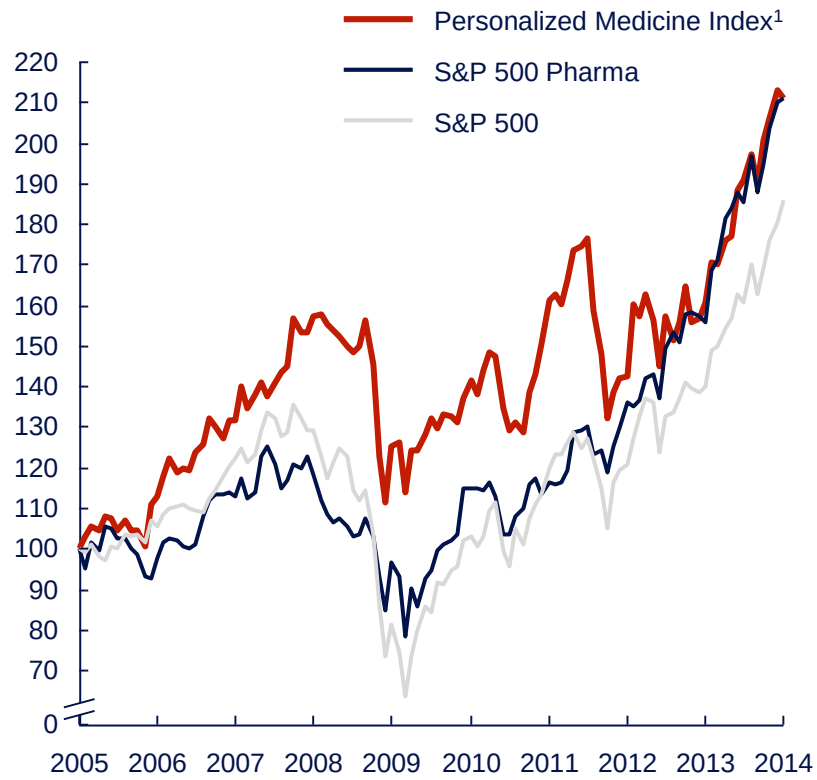
Percent of current treatments relying on biomarker data by stage of development

Percent



Investors continue to be optimistic about PM companies

Normalized to 2005 index

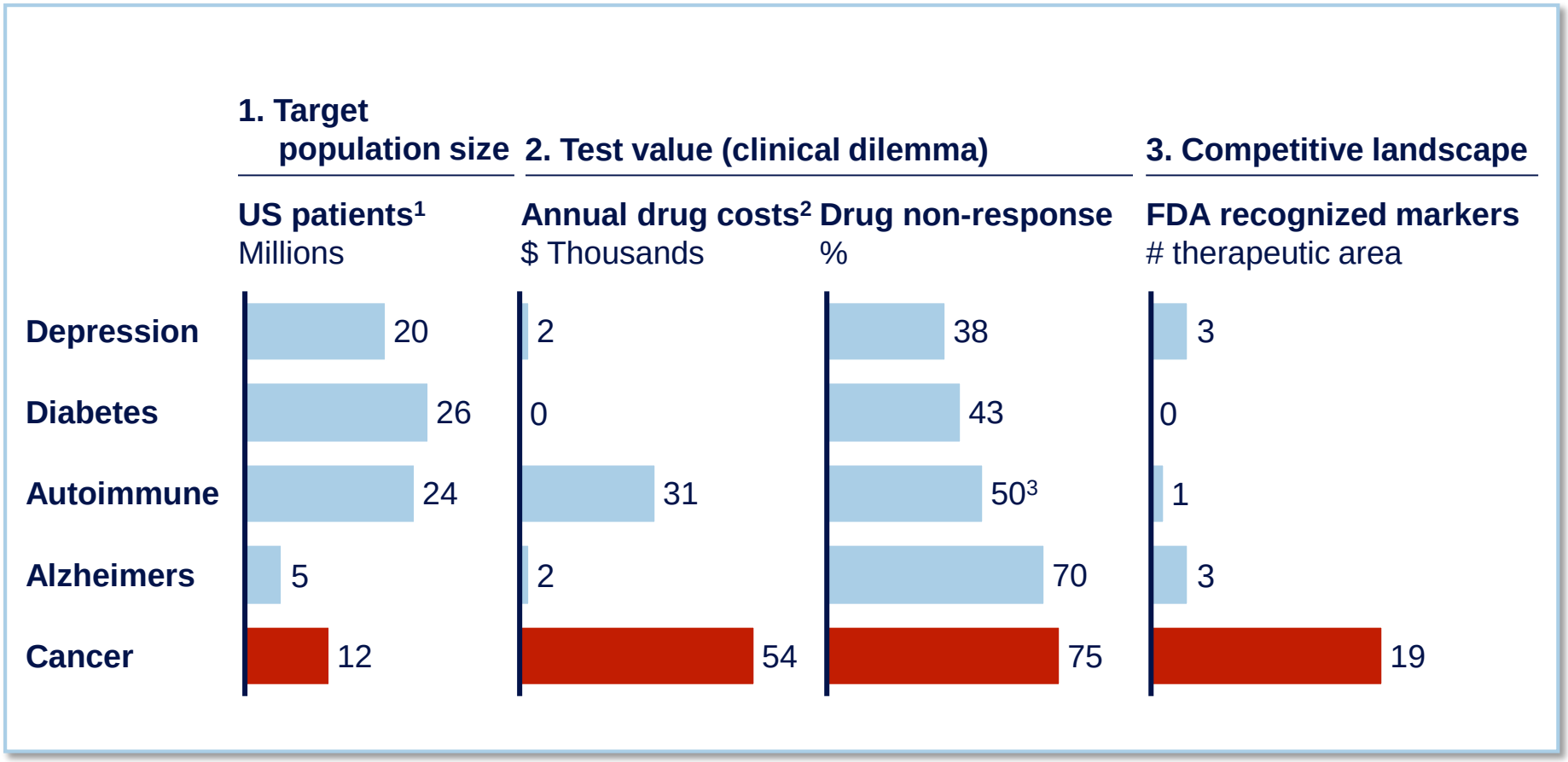


1 The Personalized Medicine Index of Public Companies consists of Becton Dickinson, Quest Diagnostics, Hologic, Laboratory Corp, Illumina, Affymetrix, Cephid, Genomic Health, Quidel, Luminex, Exact Sciences, Atossa Genetics, Celldex Therapeutics, Myriad, Qiagen, Sequenom

SOURCE: FDA, Tufts Center for Drug Development, Datastream

Significant savings potential for payors from Personalized medicine by avoiding treatment of non-responders, especially in cancer

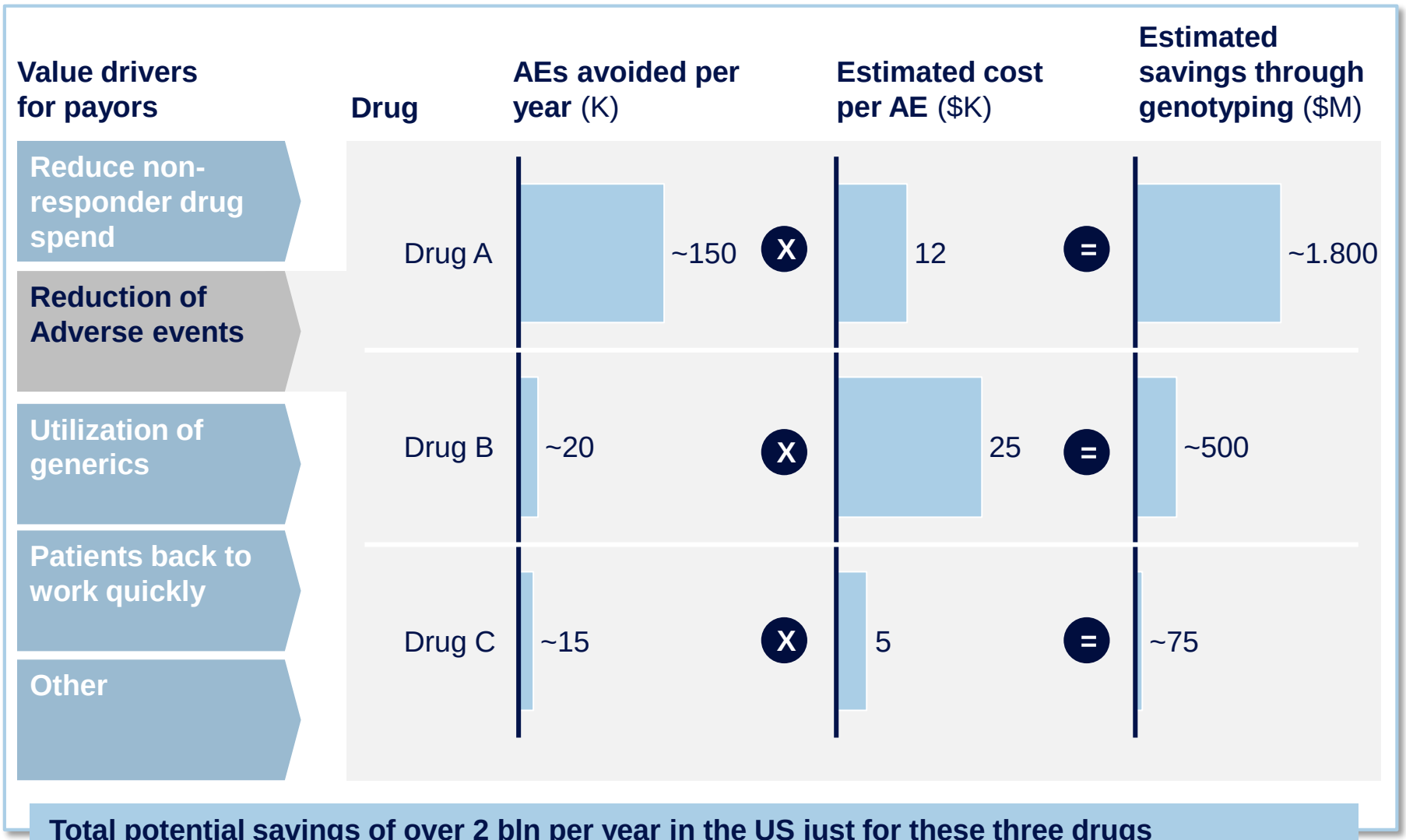
Personalized medicine value proposition in different disease areas from non-responders



1 Illustrative; All patients may not be drug eligible
2 Based on representative therapy: Paxil, Advair, Metformin, Etanercept, Namenda, Herceptin
3 Rheumatoid arthritis used as representative of autoimmune diseases

SOURCE: Case for PM 3rd generation, disease society web page, www.fda.gov

Additionally, significant savings potential for payors from personalized medicine in preventing adverse events



Total potential savings of over 2 bln per year in the US just for these three drugs

SOURCE: Provider patient population pilot in US

Setting up a central sequencing facility now for the Netherlands has clear benefits

- Also in the Netherlands application of personalized medicine is increasing
- Individual hospitals are investing in their own sequencers and are building up expertise
- It is important to take investment decisions on central vs decentral facilities early enough to avoid double costs

Benefits decentral sequencing

- **Potentially faster turn-around** time of results of individual patients
- **Easier to set** up (initially)
- **More direct influence** on the process and research by individual hospitals

Benefits central sequencing

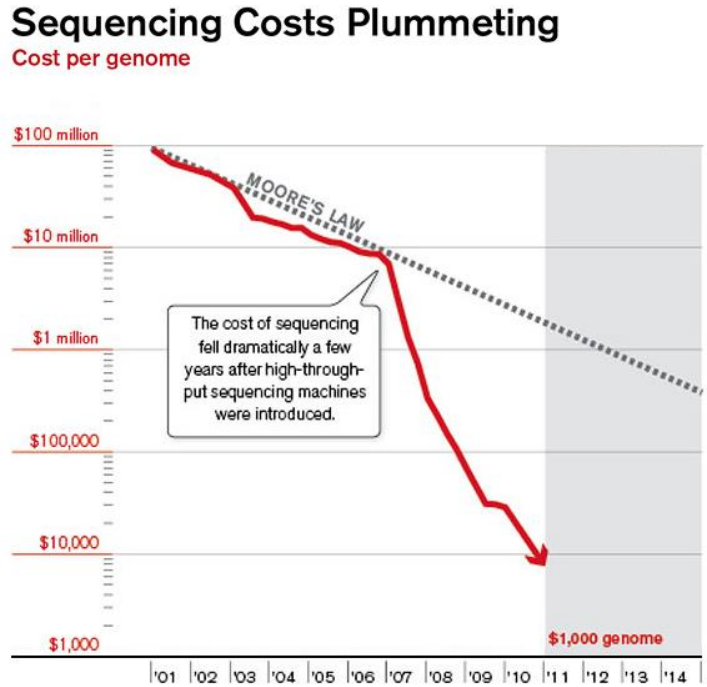
- **Faster development**, improved research results through bundling of data and expertise
- Improved **data quality** through standardization of data collection and analyses
- **Higher efficiency** and thus **lower costs**: increased utilization of expensive infrastructure and centralized expertise
- Possibility to faster **adapt quicker** to rapid technological advances (use latest equipment)
- Easier to gain **international standing**

Timing is right to set up a national center; where personalized medicine is still in the ramp up phase and most hospitals have not invested yet

What are the complexities in daily practice ?

What to measure:

Whole genome, whole exome, selected genes ?



Important considerations:

- Which genetic alterations?
- Actionable mutations
- Copy number variations
- Fusion genes
- Tumor heterogeneity
- Depth of sequencing: 100x, 500x, ultra deep?
- Cost of sequencing
- Information overload
- RNA seq

Adding to the complexity: Understanding tumor evolution

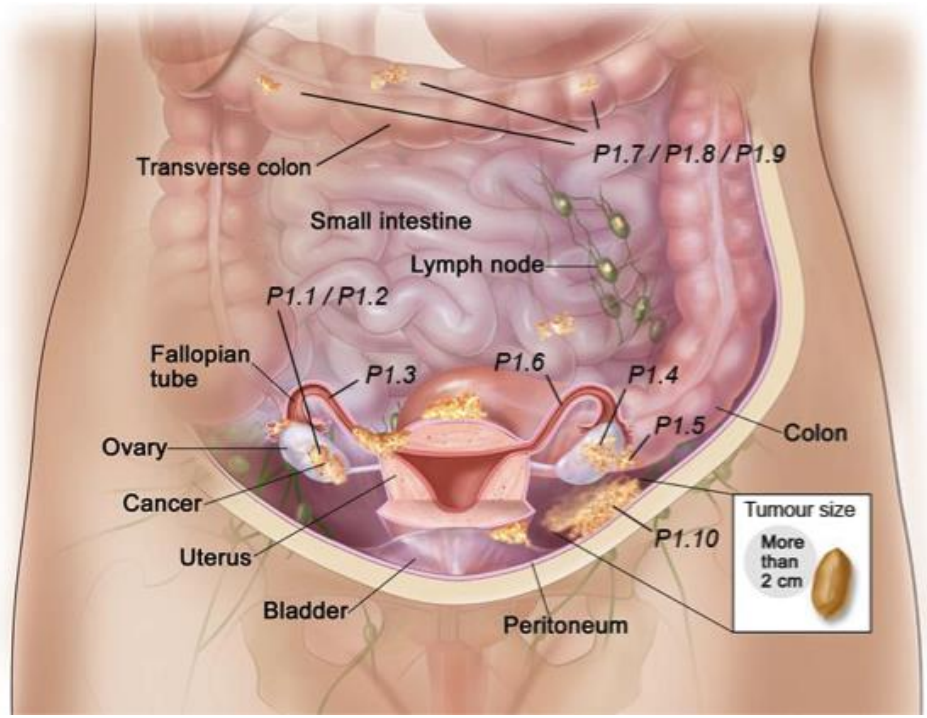
Ovarian Cancer

Simultaneous primary tumor and metastatic lesions

Treatment naïve (no selection or treatment induced effects)

Standard of care surgical cytoreduction preceding chemotherapy

High rate of relapse

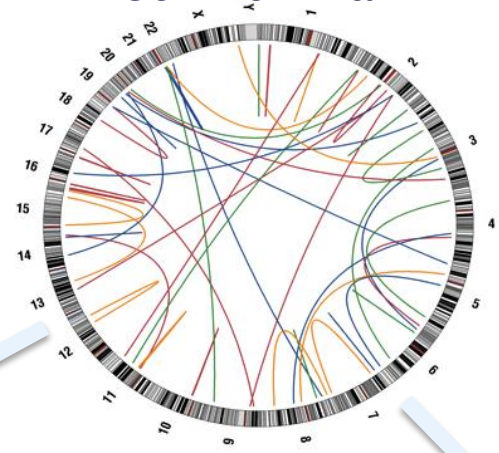


Hoogstraat et al. Genome Research, 2014

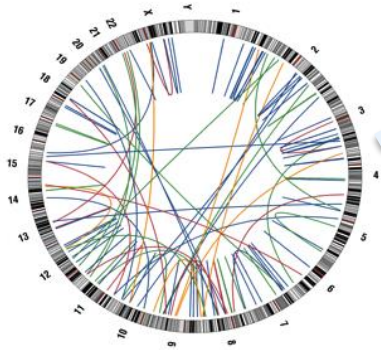
Reconstructing tumor history

Mate-pair data
1,420 somatic breakpoints

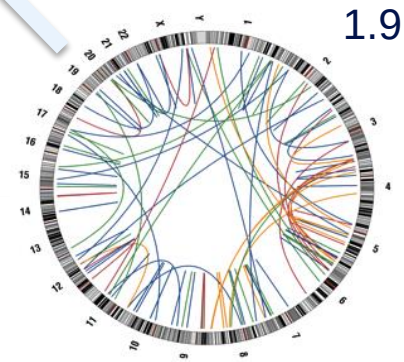
Common in all



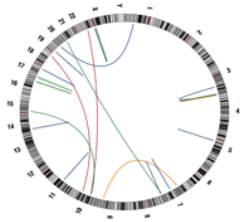
Common in
1.1, 1.2, 1.4 & 1.5



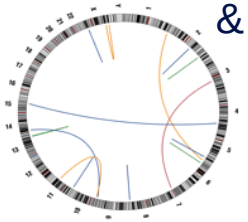
Common in 1.7, 1.8,
1.9 & 1.10



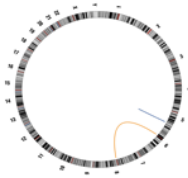
Common in 1.1
& 1.2



Common in 1.4
& 1.5



1.1



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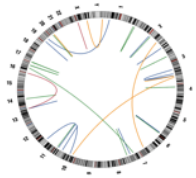

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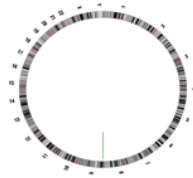
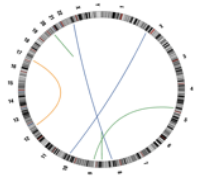


1.5



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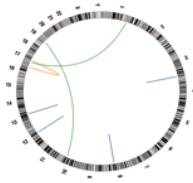

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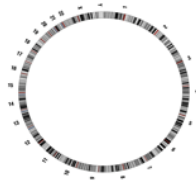

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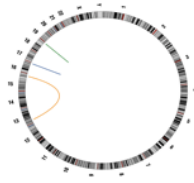
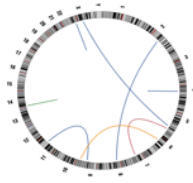


1.10

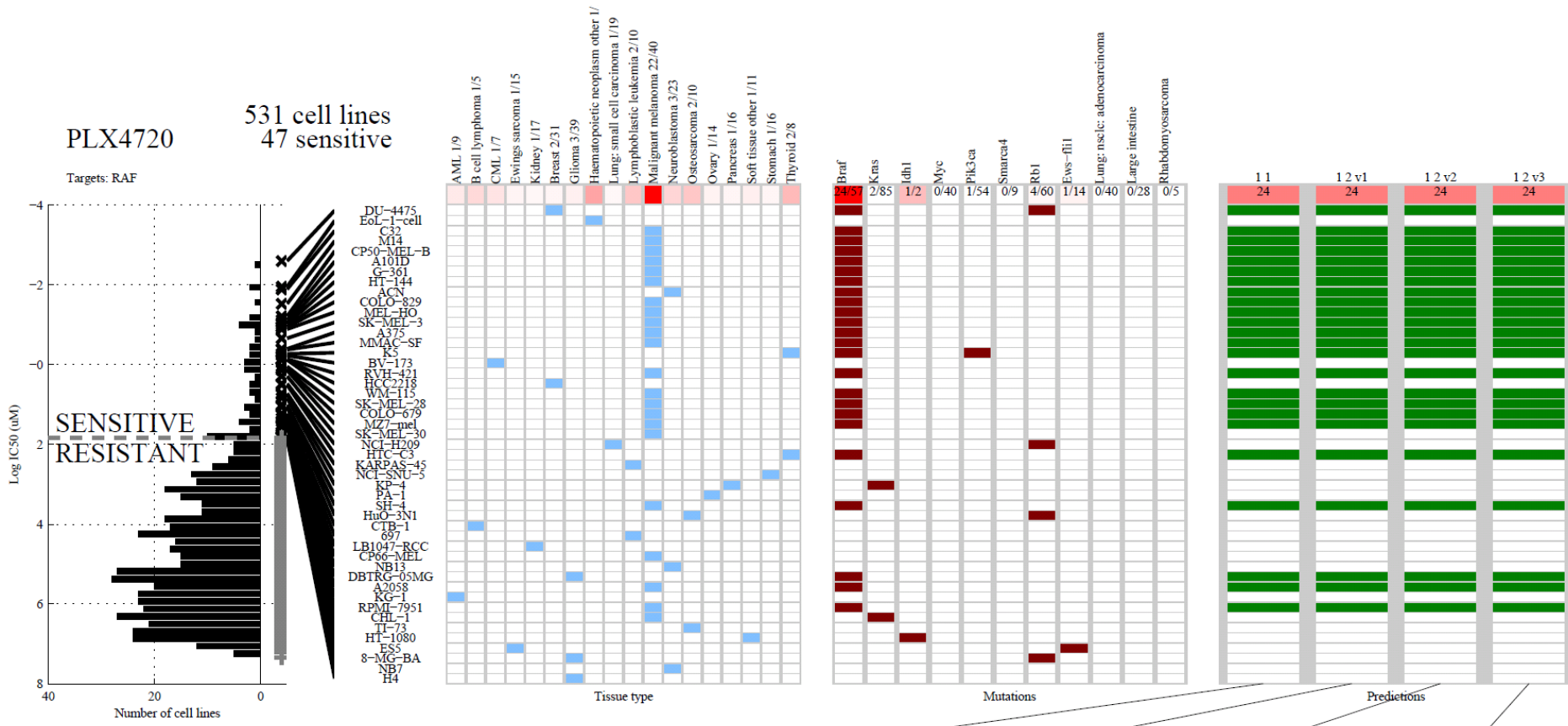


Intrapatient variability: mixed responses to treatment and the value of paired biopsies

Date sample collection	Treatment phase	Biopsy / Surgery	Material	Response to treatment	Specimen	Tumor %	Conc ng/µl	Volume	DNA yield (ng)	Remarks
12/12/11	Baseline	NA	Blood		I	NA	64	400	25600	NA
		Biopsy	Lymphnode 1		II	90	52	100	5200	Whole specimen used
5/31/12	On-treatment 1	Biopsy	Lymphnode 1	Progressive L505H	III-1	0	NA	NA	NA	NA
					III-2	50	NA	NA	NA	NA
					III-3	90	28	100	2800	Only 8 x 20 um sections used
6/14/12	On-treatment 2	Surgery	Lymphnode 1	Progressive L505H	IV-1	90	NA	NA	NA	NA
					IV-2	95	52	100	5200	Only 1 x 20 um section used
			Lymphnode 2	Stable	IV-3	90	NA	NA	NA	NA
					IV-4	90	56	100	5600	Only 1 x 20 um section used
			Lymphnode 3	Stable	IV-5	85	NA	NA	NA	NA
					IV-6	95	44	100	4400	Only 5 x 20 um sections used
8/3/12	Post-treatment	Biopsy	Lymphnode 4	Progressive	V-1	90	2.46	100	246	Only 10 x 20 um sections used
					V-2	90	17.5	100	1750	Whole specimen used
					V-3	80	NA	NA	NA	NA

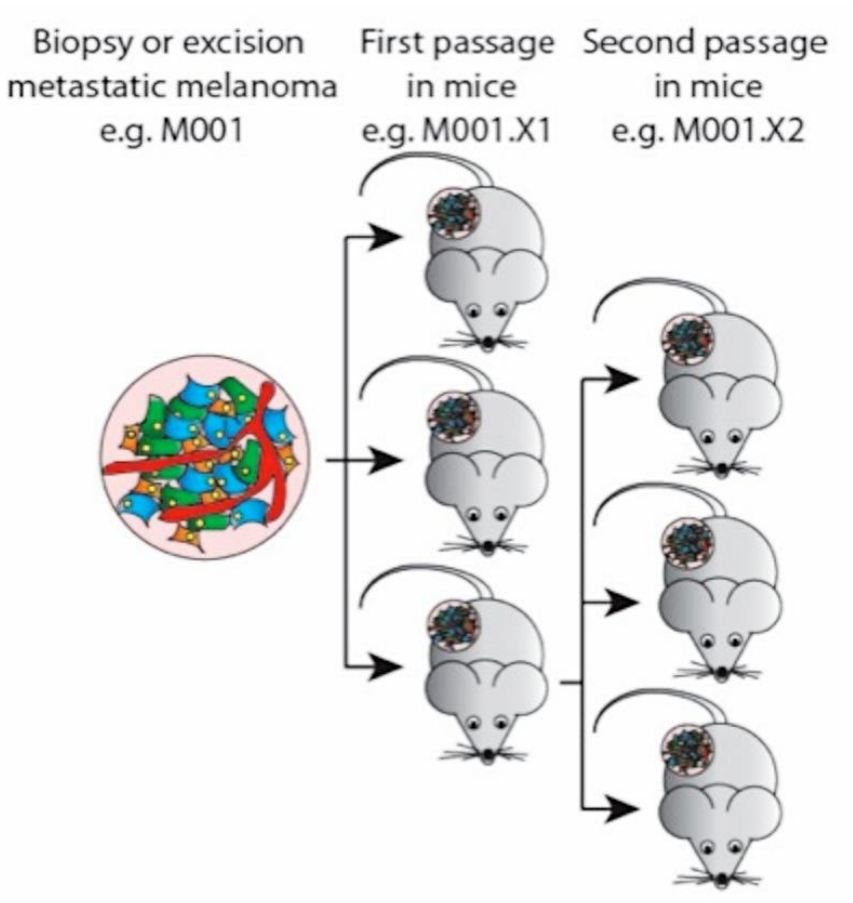
Hoogstraat et al. Unpublished data

Tissue-specific drug sensitivity

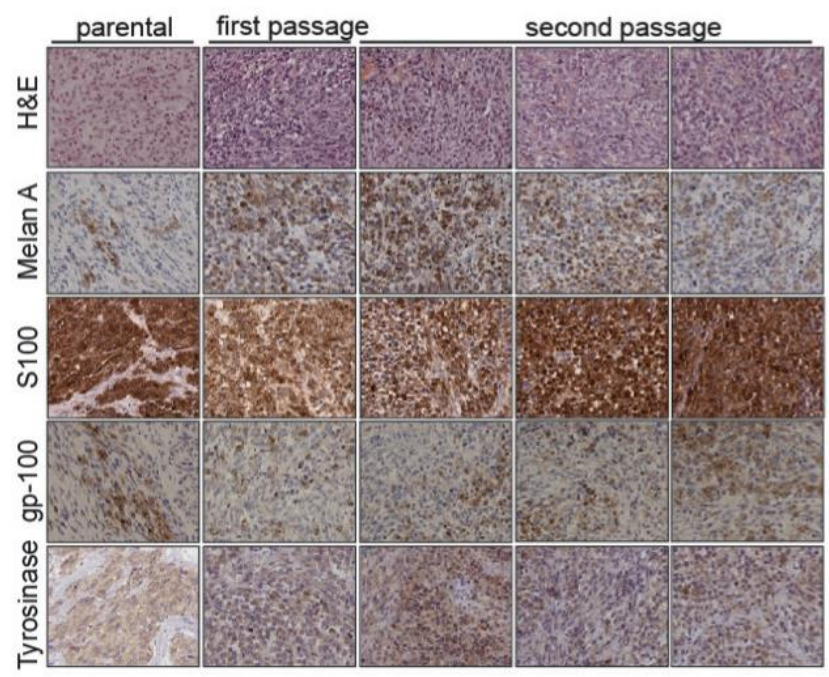


Model name	1 1	1 2 v1	1 2 v2	1 2 v3
K	1	1	1	1
M	1	2	2	2
Logic formula	BRAF	BRAF & ~lung:	BRAF & ~rhabd	BRAF & ~large
TP	24	24	24	24
FP	33	27	32	29
FN	23	23	23	23
TN	451	457	452	455
Specificity	0.93	0.94	0.93	0.94
Precision	0.42	0.47	0.43	0.45
Recall	0.51	0.51	0.51	0.51

Patient-derived melanoma xenograft program



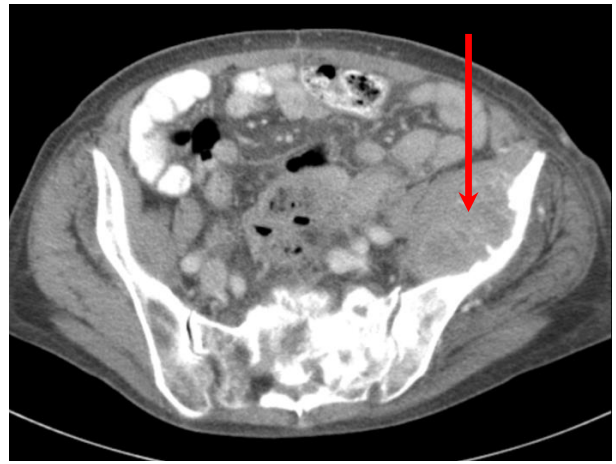
Type of sample	# of samples	Xenograft
Mutations		
BrafV600E/K	96	77 (80%)
Pre-vemurafenib	46	40(87%)
Post-vemurafenib	50	37 (74%)
NRAS Q61	10	7 (70%)
Pre-MEKi	8	6 (75%)
Post-MEKi	2	1 (50%)
BRAF WT	8	6 (75%)
Unknown	3	2 (66%)
Total all samples	117	92 (79%)



Courtesy of Daniel Peeper and John Haanen

From which tumors can organoids be generated ?

In principle all epithelial tumors: Colon, Prostate, Pancreas, Lung, Liver, Stomach, Oesophagus (developing Breast, Ovarium, Skin)



Colorectal cancer

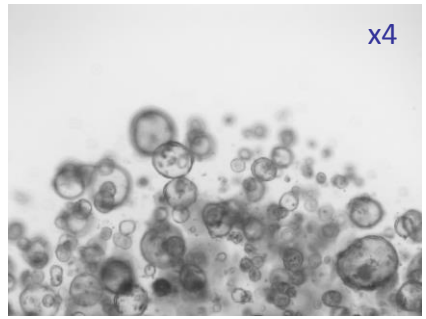
- 90-100% success rate for primary tumors
- 70% success rate for metastatic biopsy specimen (size matters!)

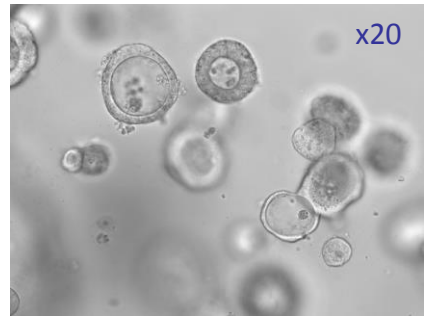
Pancreatic cancer

- 90% success rate for primary tumors
- Initial success for metastatic biopsy specimen

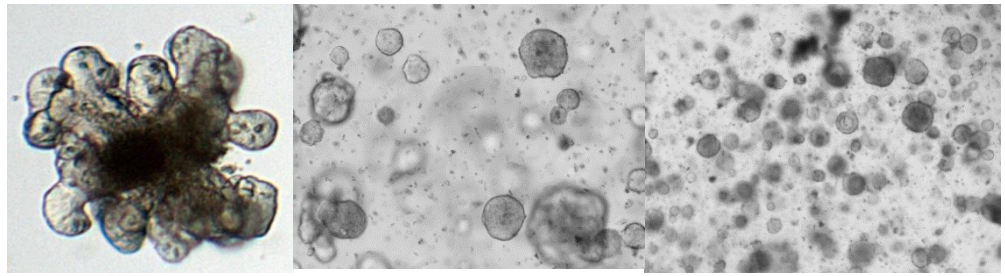
Prostate cancer

- Protocol primary tumor under development
- 25% for metastatic biopsy specimen





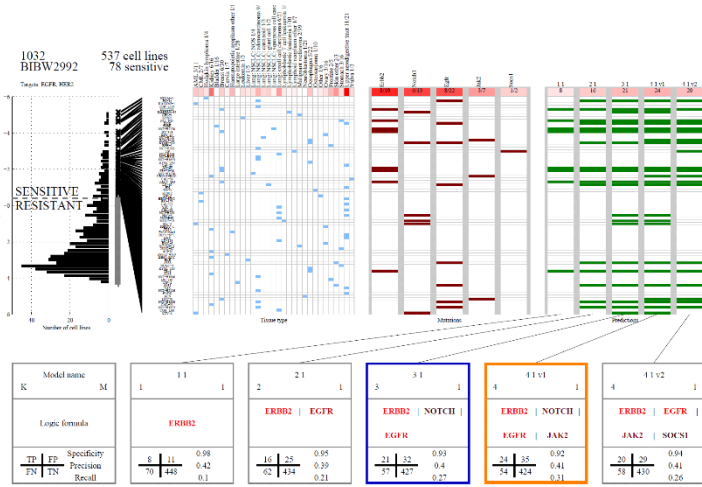
Courtesy of:
M. Van de Wetering (Hubrecht institute)
S. Boj (Hubrecht institute)
C. Sawyers (Memorial Sloan Kettering Cancer Center)



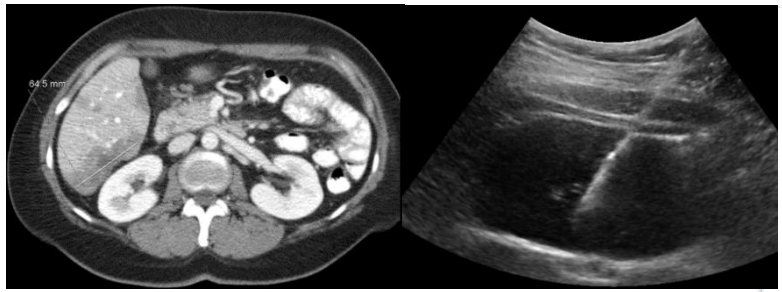
Test specific drugs on tumor organoids (and other systems?)
to confirm sensitivity

Treat patient with selected drug
Until disease progression

Center for Personalized Cancer Treatment



Bioinformatics and Systems
Biology to identify pathways



Obtain patient biopsy

Contents

- Worldwide Personalized medicine in oncology is expected to deliver significant value and will revolutionize the way patients are treated
- Adopting the new technologies of next generation sequencing will bring significant value for payors
- **CPCT is very well positioned to fulfill the need for a national sequencing center in the future**
- For successful implementation, key criteria have to be met to realize a national sequencing center

How to organize personalized cancer treatment ?

Maak uw taal keuze Nederlands

CPCT
Center for Personalized Cancer Treatment

zoeken

- Home
- Over CPCT
- Voor Patiënten
- Voor Onderzoekers
- Voor Zorgprofessionals
- Financiële Ondersteuning
- Links en Media
- Nieuws
- Contact
- Inloggen

Voor gepersonaliseerde zorg bij kanker

We weten tegenwoordig ongelooflijk veel meer over hoe kanker werkt, maar helaas heeft dat nog niet geleid tot grote veranderingen in de manier waarop we kanker kunnen behandelen. Dit komt in grote mate doordat we nog steeds een behandeling kiezen die voor de meeste mensen met dezelfde vorm van kanker werkt en niet is afgestemd op de individuele patiënt. Het Center for Personalized Cancer Treatment (CPCT) probeert hier verandering in te brengen door het genetische materiaal, het DNA, op een dusdanige manier te analyseren aan het begin van het behandeltraject zodat in de toekomst voor elke patiënt een behandeling op maat kan worden aangeboden.

QUICKLINKS

- > Voor patienten
- > Voor onderzoekers
- > Voor zorgprofessionals
- > Inloggen

NIEUWS

read more >

read more >

Bent u een
Patiënt

Bent u een
Zorgprofessional

Bent u een
Onderzoeker

CPCT is very well positioned to set up a national sequencing center given its achievements in the recent years

Selected quotes from interviews

CPCT achievements to date

- Set up of Multi-disciplinary Expert Board
- Setup initial ICT infrastructure (data in EZIS, eCRF, Biobank, sequencing database)
- Two track system for diagnosis
- 1,240 patients included of which ~957[1] samples sequenced, 889 Molecular Pathology Reports generated
- Treatment data available for 470 samples
- Increasing number of Dutch hospitals (UMCs and STZs) interested in joining the CPCT
- International attention for CPCT, especially from the US (e.g. off-label program ASCO)

"PR and (international) visibility very good"

"CPCT has a vision and is ambitious"

"CPCT very good in attracting financing"

1 586 samples sequenced using SoLiD for ~2000 mutations, 489 sequenced using IonTorrent for ~50 mutations by June 2014, individual samples can be sequenced using both techniques

SOURCE: Interviews, CPCT

The (near-future) ambition will focus on making sequencing available to all cancer patients, enabling personalized therapy and facilitating research

Ambition

"We aim to become the first non-profit nationwide (oncology) sequencing and treatment advice center, connecting all hospitals to bring personalized medicine to all Dutch patients"

Make sequencing data available to all patients

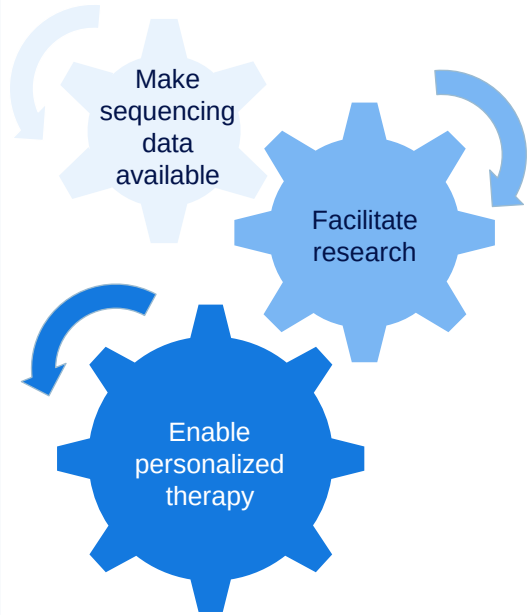
- Embed CPCT in routine diagnosis, making sequencing timely and safely available to all metastatic cancer patients
- Combine clinical and genetic data in database (bring together data for all ~17.000 cancer patients per year within 6 years)

Facilitate research

- Enable patients to participate in clinical trials (X per year) with novel (combinations of) drugs
- Improve trial (and treatment) success through improved patient stratification using DNA-based biomarkers
- Facilitate translational research by making gathered data available to leading scientists and international collaborations (15 publications/yr)

Enable personalized therapy

- Accelerate and improve the application of personalized treatment using tumor genetic profiling:
  - Apply already available (targeted) treatments more effectively
  - Significantly reduce incidence of ineffective treatments (reduction by 5% by 2020)



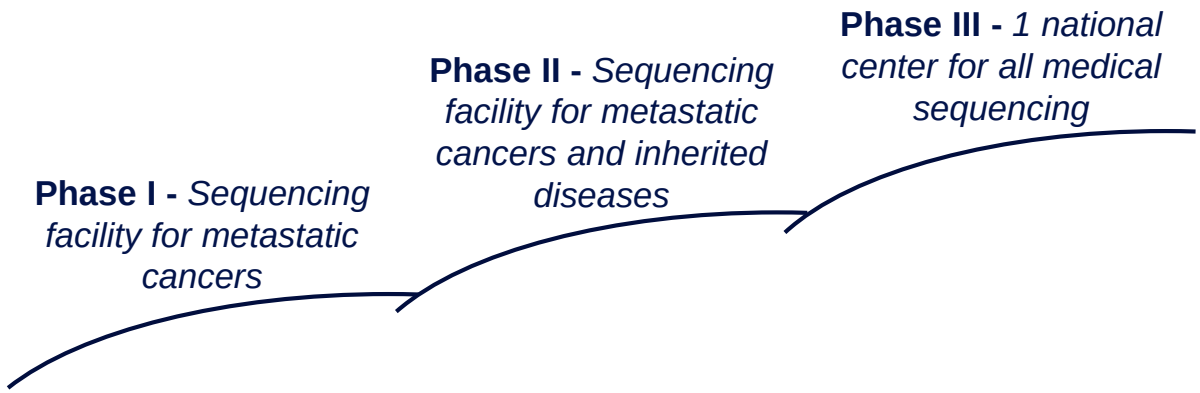
SOURCE: CPCT

Over time, the mission may evolve to encompass all medical-related sequencing tests and patients

ILLUSTRATIVE

Focus of this document

Center for personalized cancer treatment could over time evolve into a "National Medical Sequencing Center"



	Phase I - *Sequencing facility for metastatic cancers*	Phase II - *Sequencing facility for metastatic cancers and inherited diseases*	Phase III - *1 national center for all medical sequencing*
Sequencing targets	▪ Primary focus: metastatic cancers for whom targeted treatments are available ▪ Start with other metastatic cancers	▪ All metastatic cancers (also using RNA-Seq to reduce unnecessary treatment incidence) ▪ Clinical genetics for inherited and/or other diseases	▪ Cancer profiling, both primary, hematologic and metastatic ▪ Clinical genetics for inherited and/or other diseases
Number of patients (2020[1])	**<17k**	**~23k**	**>45k**

1 Assuming 23% of cancer patients can be and want to be included

SOURCE: CPCT, 2014

Personalized medicine consists of a chain of activities

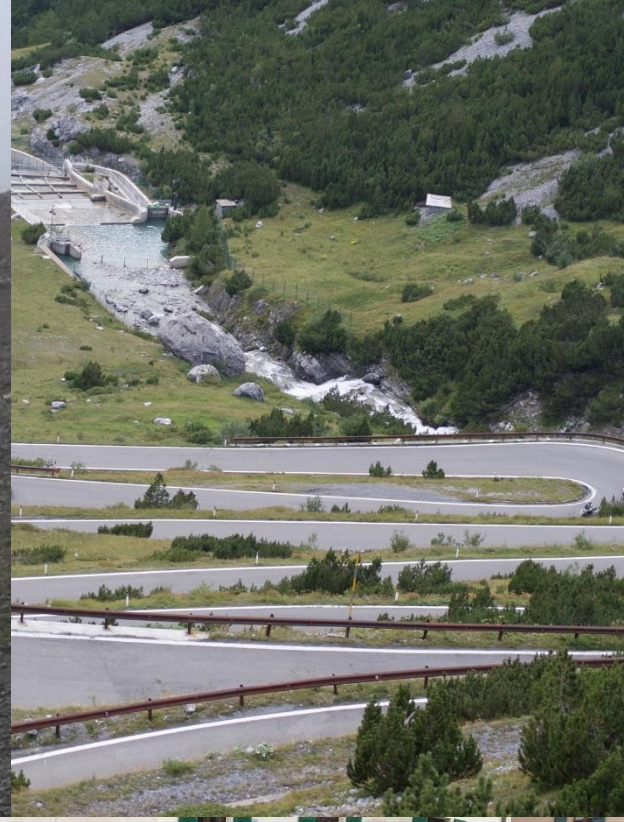
	Including patients	Collecting clinical data	Taking biopsies[1]	Preprocessing biopsies[1]	Sequencing DNA of biopsies[1]
Value chain					
Key success factors	▪ Interpersonal skills to engage with patients ▪ Standardized protocols ▪ Physicians engagement and motivation to include patients	▪ Standardized list of questions/ forms to collect clinical data ▪ Uniform process of collecting data ▪ Certification??	▪ Technical skills to take biopsies based on high volume of patients ▪ Quality and usability of medical equipment to take biopsies	▪ Technical skills based on high volume of samples ▪ Quality and usability of equipment ▪ Knowledge for interpretation of samples	▪ High utilization rate of infrastructure ▪ Fast throughput times ▪ Procurement power to bargain lower prices ▪ Strict protocols and standards ▪ Agile response to new innovations ▪ Low maintenance costs
Who?	☑ Hospital / doctors ☐ CPCT	☑ Hospital / doctors ☐ CPCT	☑ Hospital / doctors ☐ CPCT	☐ Hospital / pathologists ☑ CPCT (for samples to be sequenced by CPCT)	☐ Third parties ☑ CPCT

Personalized medicine consists of a chain of activities

	Managing sequence and clinical data in database, and reporting	Analyzing database for new treatment and non-treatment options	Conducting clinical trials	Storage of tissue[1] (biobank)
Value chain				
Key success factors	▪ Easy to use, intuitive user interface ▪ Compatibility with different input and outputs ▪ Low maintenance costs ▪ High quality of data ▪ Multiple ways to analyze data	▪ Large amounts of data ▪ High data quality ▪ Talent to identify new options ▪ Fast translation into new trial setups ▪ Multidisciplinary approach and network	▪ Access to large pool of patients ▪ Access to funding (e.g. pharma companies) ▪ Clear and easy to use protocols	▪ Efficient storage and retrieval proces
Who?	☐ Third parties ☑ CPCT	☑ Medical centers/ Researchers/ Pharma ☐ CPCT (approves data mining initiatives)	☑ Medical centers / Researchers/ Pharma ☐ CPCT	☑ Medical centers ☐ CPCT

Participating centers and acknowledgements


Comune di BORMIO
Passo dello Stelvio
m. 2758 s.l.m.




BARCODE FORLIFE
Stelvio for Life
Overwin de boeiendste berg en help een Kankerpatiënt
Cheque
€ 273.514,99
aangeboden aan Barcode for Life 30 augustus 2014

Acknowledgements

UMC Utrecht
Geert Cirkel
Christa Gadellaa
Marlies Langenberg
Edwin Cuppen
Ies Nijman
Paul van Diest
Stefan Willems
Maurice van den Bosch
Marijn van Leeuwen
Wouter Veldhuis
Ida van Belle
Marco Koudijs
Sjoerd Elias
Nicolle Besselink
Stef van Lieshout
Roelien Kronemeijer
Joline Claassen
Ciska de Ruijter

NKI-AvL
Emile Voest
Marlous Hoogstraat
Neeltje Steeghs
Jan Schellens
Emmy Harms
Marianne Keessen
Mariska Zengerik
Henk Botma
Harm van Tinteren
Rene Bernards
Jelle ten Hoeve

Erasmus MC
Sander Bins
Martijn Lolkema
Judith Reinders
Patricia de Vos
Wilma Keller
Maja de Jonge
Stefan Sleijfer
John Martens