Lessons Learned from a Decade of Precision Medicine: Where do We Go from Here?

Lillian L. Siu, MD

Princess Margaret Cancer Centre, Toronto, Canada

BMO Chair in Precision Genomics

Disclosures (2015-2016)

I have the following financial relationships to disclose:

Consultant for: **Boerhinger-Ingelheim (uncompensated), Merck (compensated), Pfizer (compensated), Celgene (compensated)**

Speaker's Bureau for: None

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Stockholder in: None

Honoraria from: None

Employee of: None

Contrasting Old and New Medicine

Old Medicine	New Medicine
Population-Based	Individualized
One-Off, Doctor's Office	Real-Time Streaming, Real World
Doctor Ordered Data	Patient Generated Data
Doctor's Notes, Unshared	Our Notes, Patient Edited
Information Owned by Doctors and Hospitals	Information Owned by Rightful Owner
Expensive, Big-Ticket Tech	Cheap Chips, Moore's Law
Data Limited	Panoromic

@Eric Topol Twitter

Vision for a **Triad of Synergy** to form a **Precision Medicine Enterprise**
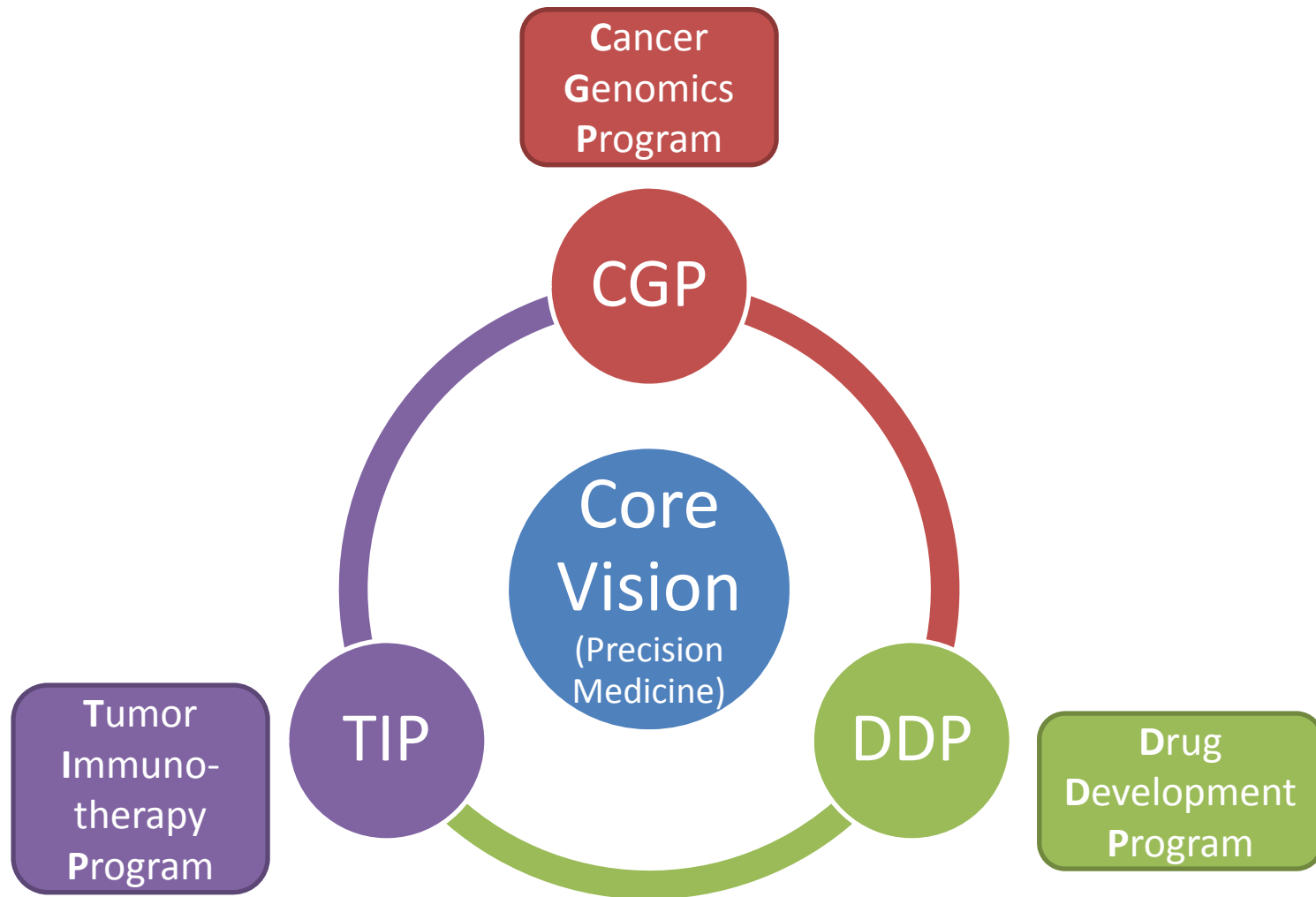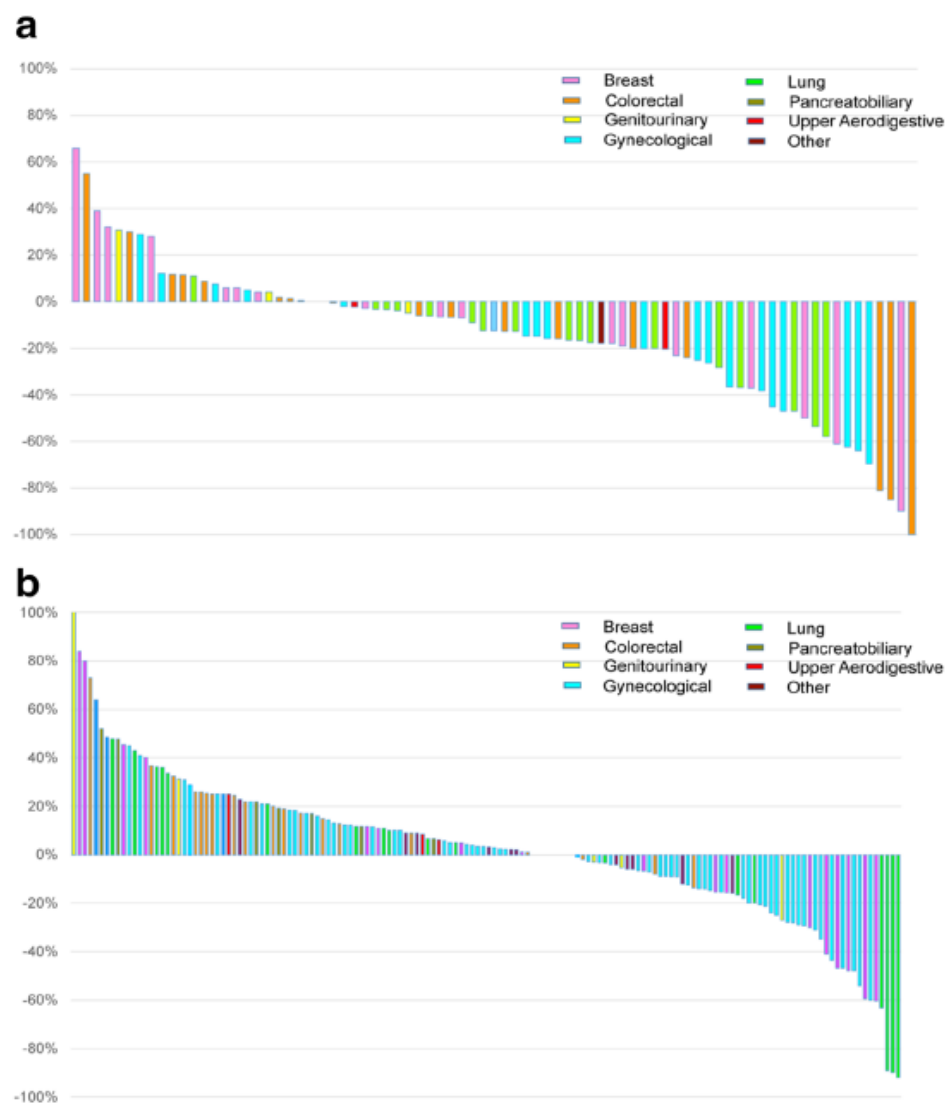
Selected Molecular Profiling Initiatives and Genotype-Matching to Clinical Trials

Group	Sample Size	Platform	Fresh Biopsy vs FFPE	Germ-line Control	Number and % of "Matched" Patients in Genotype-Matched Clinical Trials
Gustave Roussy MOSCATO	1,035	40-75 gene panels (Life) + CGH (Agilent) + RNA Seq	Fresh biopsy	Yes	199/1035 = **19%**
Institut Curie	741	46 gene panel (Life) + CNA (Affymetrix) +IHC	Fresh biopsy	No	195 randomized/741 = **26%**
BCCA	100	Whole genome	Fresh biopsy	Yes	1/100 = **1%**
MD Anderson	2,000	11-50 gene panels (Life)	FFPE	No	83/2000 = **4%**
Princess Margaret	1,640	23-48 gene panels (Ilumina, Life)	FFPE	Yes	92/1640 = **5.6%**

CNA = Copy number alterations; IHC = Immunohistochemistry

Massard et al. Cancer Dis 2017; LeTourneau et al. Lancet Oncol 2015; Laskin et al. Cold Spring Harb Mol Stud 2015; Meric-Bernstam et al. J Clin Oncol 2015; Stockley, Bedard et al. Genome Med 2016.
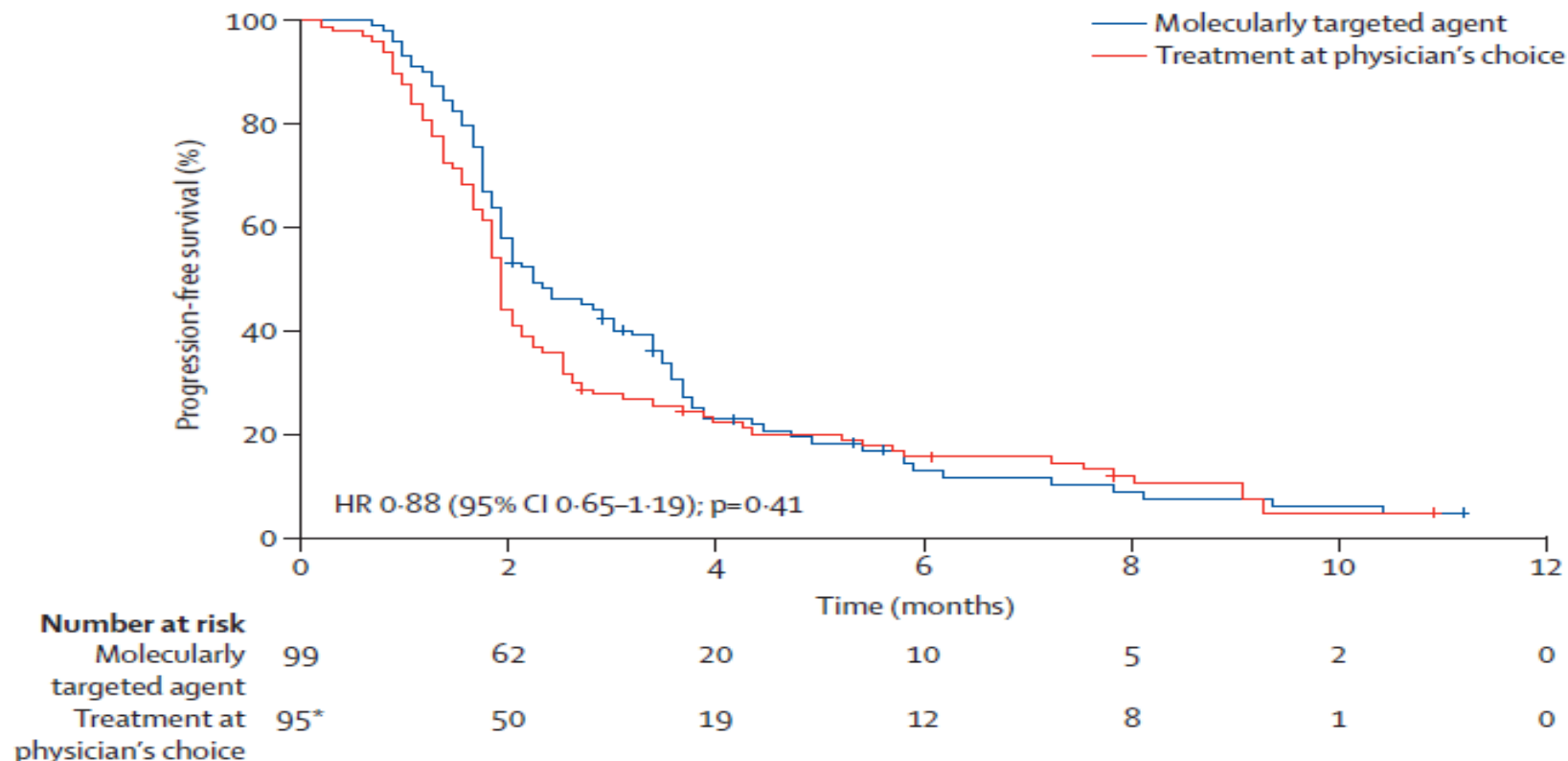
IMPACT/COMPACT Genotype-Matching to Trials

a

Legend: Breast, Colorectal, Genitourinary, Gynecological, Lung, Pancreatobiliary, Upper Aerodigestive, Other

Genotype-matched ORR = 19%

b

Legend: Breast, Colorectal, Genitourinary, Gynecological, Lung, Pancreatobiliary, Upper Aerodigestive, Other

Stockley, Bedard et al. Genome Med 2016.

Genotype-unmatched ORR = 9%

Fig. 4 a *Waterfall plot* of best tumor shrinkage of target lesions by RECIST for patients treated on (**a**) genotype-matched clinical trials (n = 79) and (**b**) genotype-unmatched clinical trials (n = 150)

SHIVA Trial

Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

Progression-free survival (%) vs Time (months)

Legend:
— Molecularly targeted agent
— Treatment at physician's choice

HR 0·88 (95% CI 0·65–1·19); p=0·41

Number at risk						
Molecularly targeted agent	99	62	20	10	5	2	0
Treatment at physician's choice	95*	50	19	12	8	1	0

Limits to Personalized Cancer Medicine

Ian F. Tannock, M.D., Ph.D., and John A. Hickman, D.Sc.
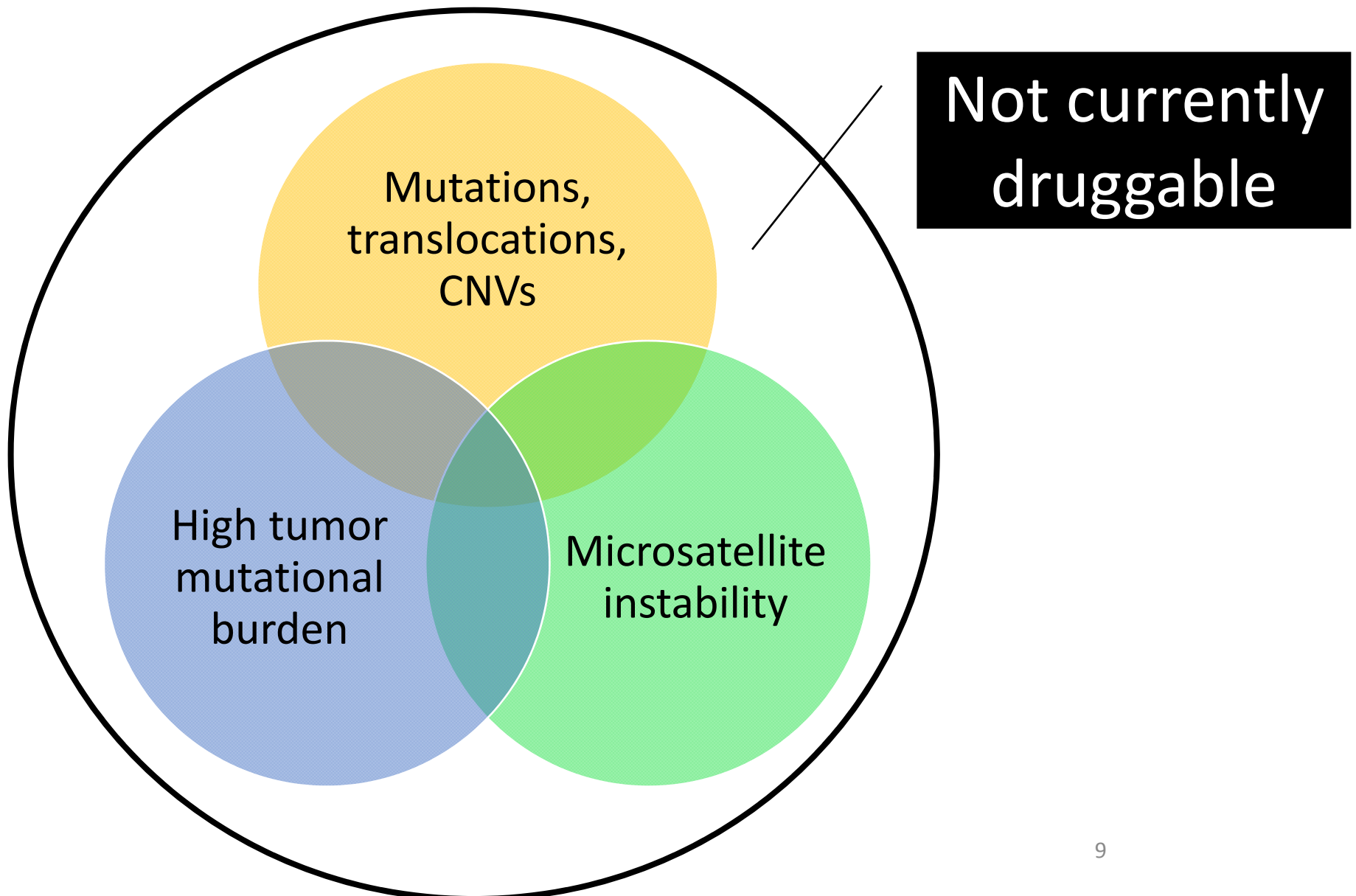
PRECISION MEDICINE | OUTLOOK

PERSPECTIVE

The precision-oncology illusion

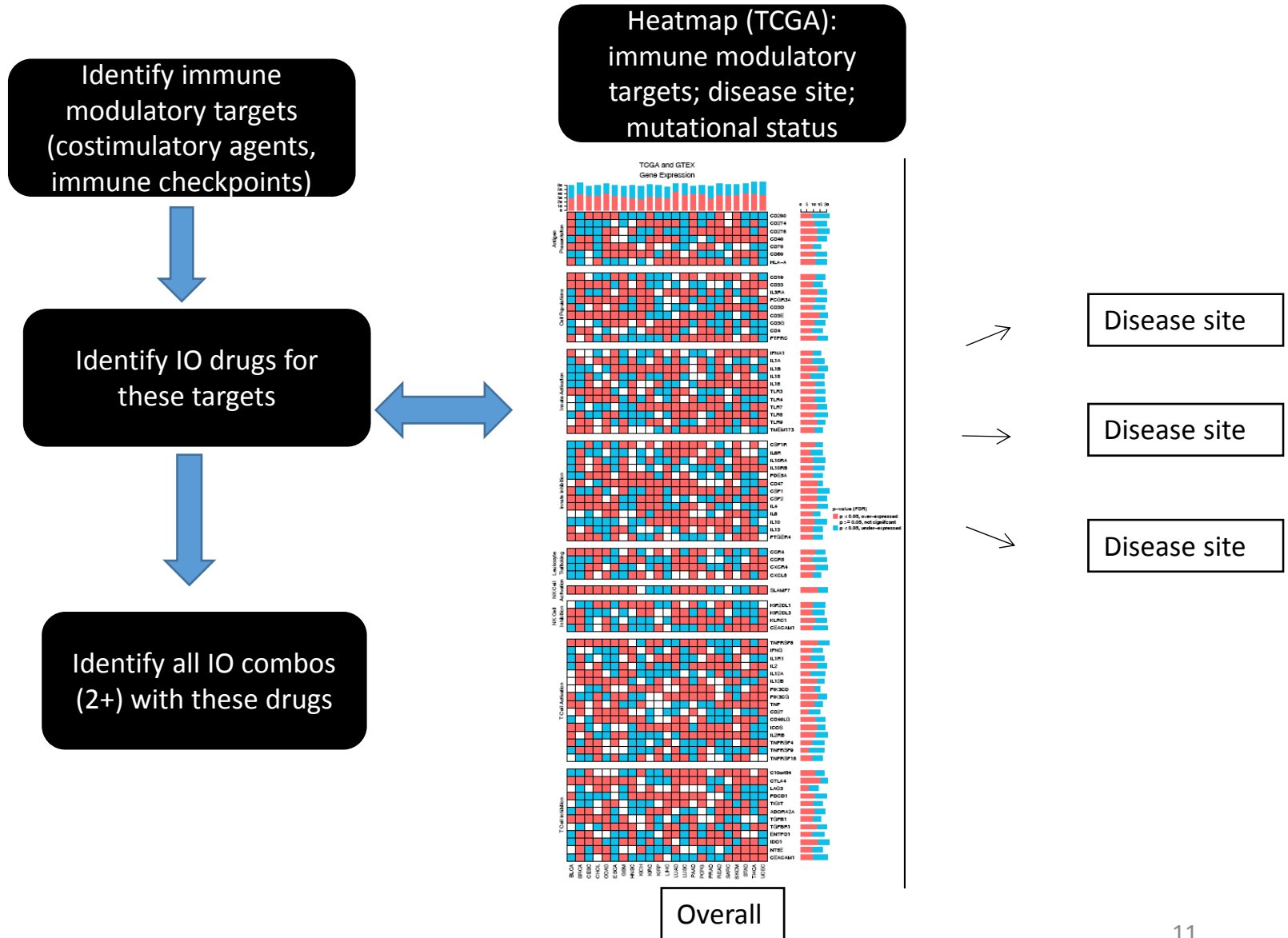Precision oncology has not been shown to work, and perhaps it never will, says **Vinay Prasad**.
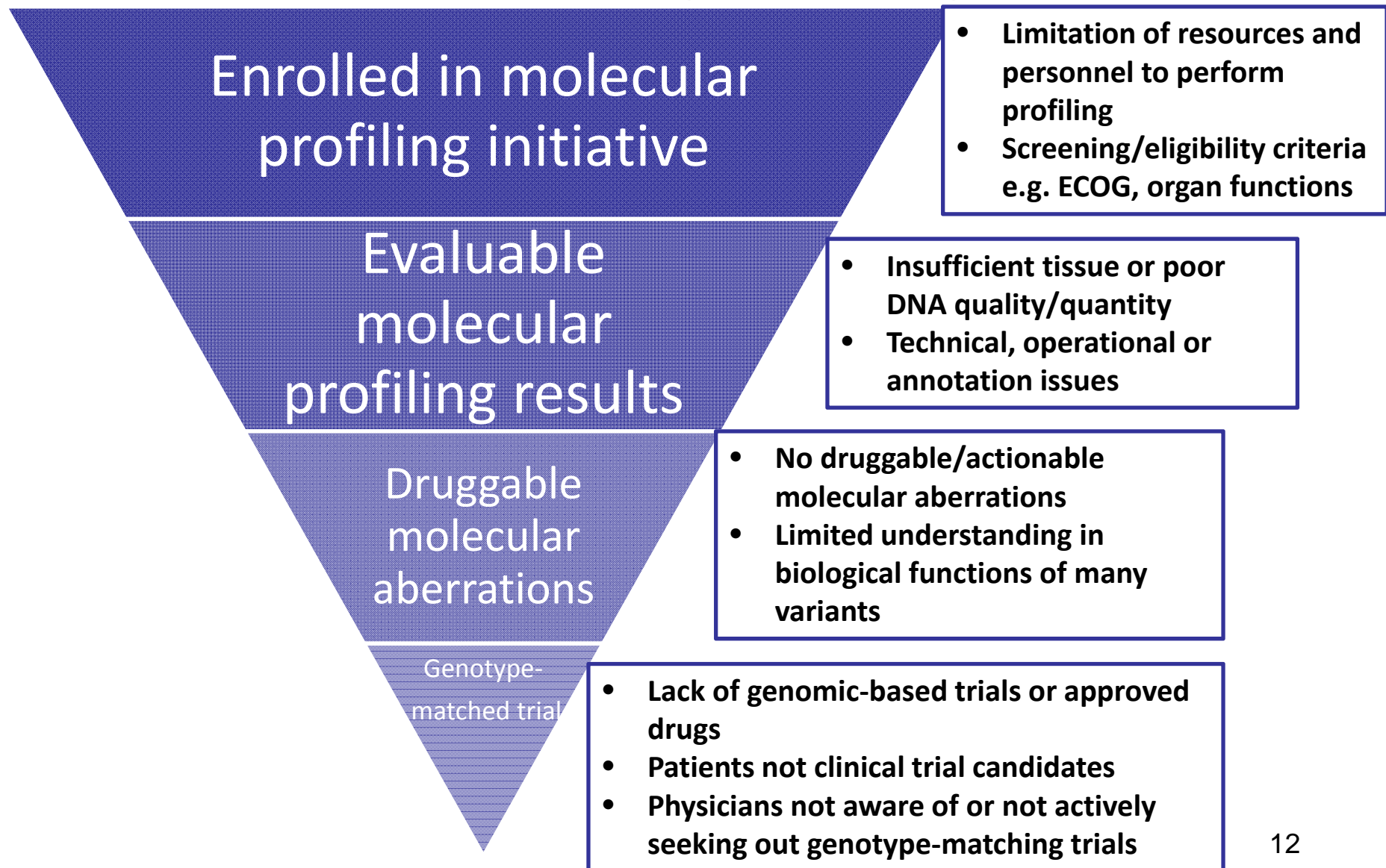
What can be "druggble" from NGS?

If we ran 2,039 TCGA (lung, breast, gyn) Samples on Hi5 Panel, 87% have Aberration of an Actionable Pipeline Gene from Company X

Entities	Actionable genes	Mutant tumors
MEK	*KRAS, NRAS, MAP2K1, NF1*	17%
BRAF+MEK	*BRAF*	3%
ERK	*KRAS, NRAS, MAP2K1, NF1, BRAF, ARAF*	20%
pan-PI3K	*PIK3CA, INPP4B, PTEN, PIK3R1*	54%
AKT	*AKT1, AKT2, AKT3*	3%
PI3Kα	*PIK3CA*	27%
SMO	*SMO*	1%
SERD	*ESR1*	1%
ALK	*ALK*	3%
HER2 dimerization	*ERBB2, ERBB3*	4%
HER3	*ERBB3*	2%
Immunotherapies (PDL-1, CTLA-4, PD-1, OX40, STAT3, CXCR2)	High mutation rate tumors	21%

In Silico Analysis to Identify Rational IO Drug Combinations

Attrition in Molecular Profiling and Genotype-Drug Matching

Enrolled in molecular profiling initiative

- **Limitation of resources and personnel to perform profiling**
- **Screening/eligibility criteria e.g. ECOG, organ functions**

Evaluable molecular profiling results

- **Insufficient tissue or poor DNA quality/quantity**
- **Technical, operational or annotation issues**

Druggable molecular aberrations

- **No druggable/actionable molecular aberrations**
- **Limited understanding in biological functions of many variants**

Genotype-matched trial

- **Lack of genomic-based trials or approved drugs**
- **Patients not clinical trial candidates**
- **Physicians not aware of or not actively seeking out genotype-matching trials**

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What are the Gaps?

- Genomic approaches are limited:
  - Most of the kinome is not druggable
  - Even if druggable, a suitable clinical trial may not be available
- Collaboration with others to increase power of identifying rare variants
- Going beyond genomics:
  - Other omics
  - Functional testing
- Addressing heterogeneity and evolution
- Data sharing

Consent Form – Data Sharing Language

Study Information and Consent Form

Ontario-wide **C**ancer **TA**rgeted **N**ucleic acid **E**valuation

Study ID: OCTANE

Your targeted gene sequencing results, along with limited clinical information that does not identify you as an individual, such as your age, gender, cancer type, and pathology information related to the samples tested, and your survival time will be sent to centralized scientific databases or shared with collaborating researchers outside of this hospital.
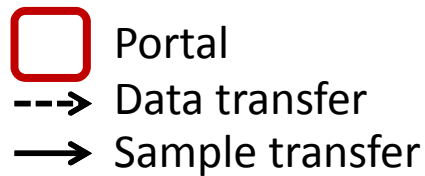
Data from this study can be shared through two types of databases: open-access or controlled-access. An open-access database is publicly accessible and contains limited clinical information and analyses of samples. A controlled-access database contains more detailed clinical information, such as your relevant past medical history and the results of your prior and ongoing cancer treatments, and analyses of samples, but is only accessible to researchers who sign agreements defining how data may be used. All data will be stripped of all personal identifying information. Your name, address, and telephone number will NOT be put into either database.

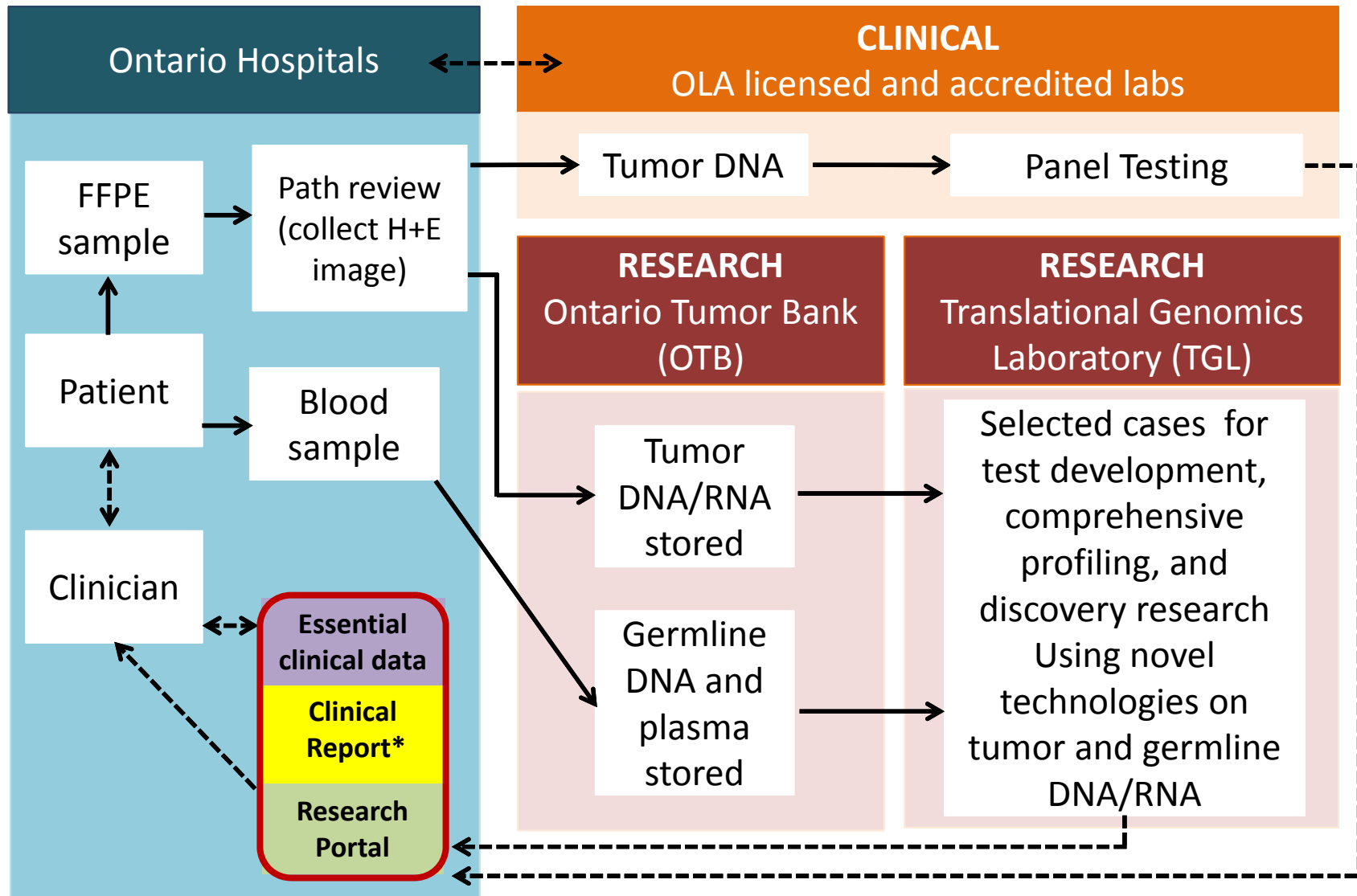# Ontario-wide Cancer Targeted Nucleic acid Evaluation (OCTANE)
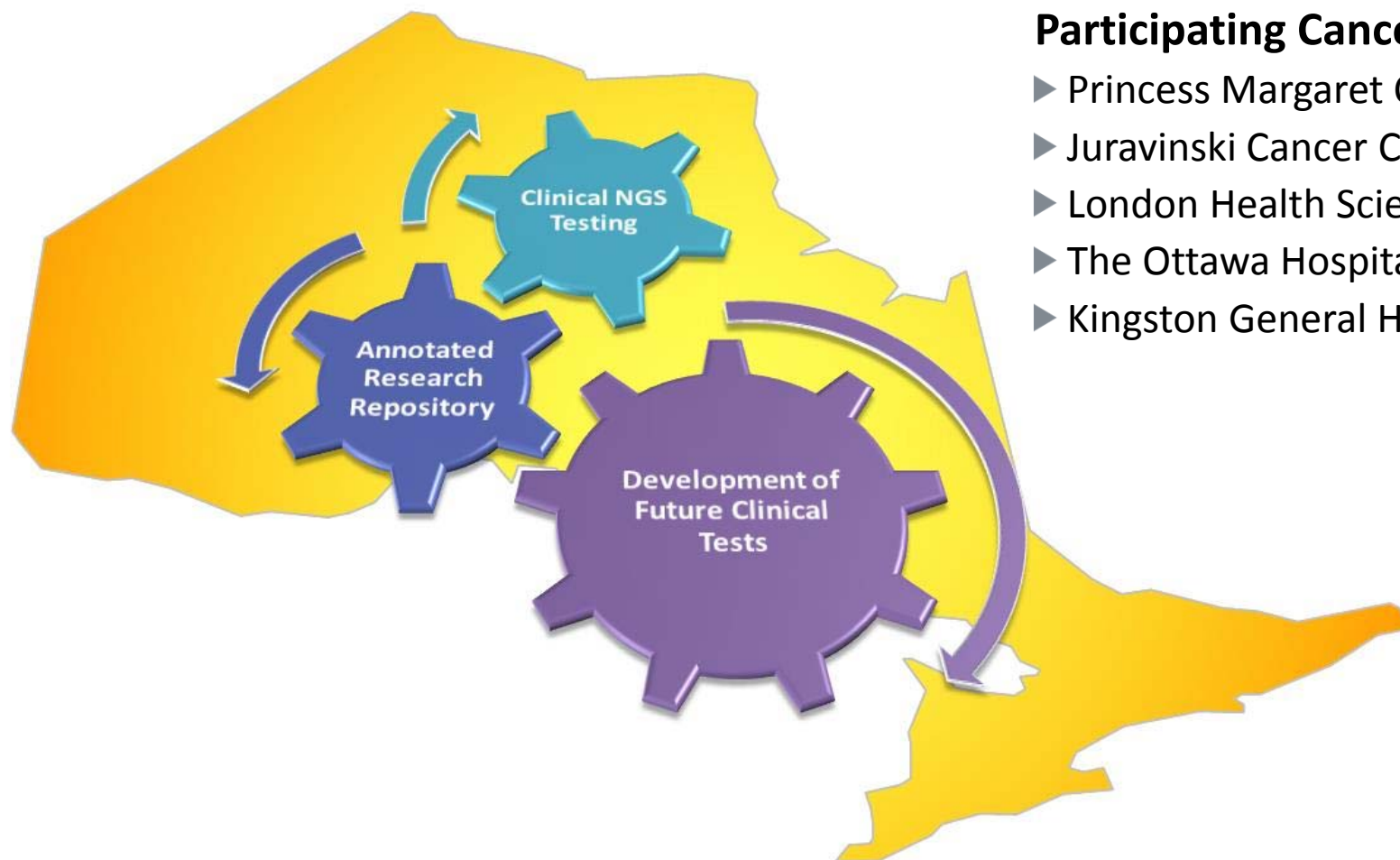
Participating Cancer Centres

▶ Princess Margaret Cancer Centre

▶ Juravinski Cancer Centre

▶ London Health Sciences Centre

▶ The Ottawa Hospital

▶ Kingston General Hospital

OCTANE Study Process

Legend:
- ⬜ (red box) Portal
- – – → Data transfer
- ──→ Sample transfer

Ontario Hospitals

CLINICAL
OLA licensed and accredited labs

FFPE sample → Path review (collect H+E image)

Patient

Blood sample

Clinician

Path review → Tumor DNA → Panel Testing

Portal (red box):
- Essential clinical data
- Clinical Report*
- Research Portal

RESEARCH
Ontario Tumor Bank (OTB)

RESEARCH
Translational Genomics Laboratory (TGL)

Tumor DNA/RNA stored

Germline DNA and plasma stored

Selected cases for test development, comprehensive profiling, and discovery research Using novel technologies on tumor and germline DNA/RNA

*Clinical report for lung, CRC, and melanoma patients only

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CAPTUR – CAnadian Profiling and Targeted Agent Utilization Trial

CAPTUR Trial Design

ACADEMIC INSTITUTIONS

Profiled Patients (n = 1000-/y)

Druggable

Non-Druggable

?

Genomic Profiling Groups
- **POG/BC**
- **OCTANE/ON**
- **Exactis/QB**
- **PROFYLE Pediatric**

CCTG

Single Agent Matching (max = 24 pts/cohort)

Full clinical data
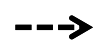
Full genomic data

PHARMA

Drugs and Funding
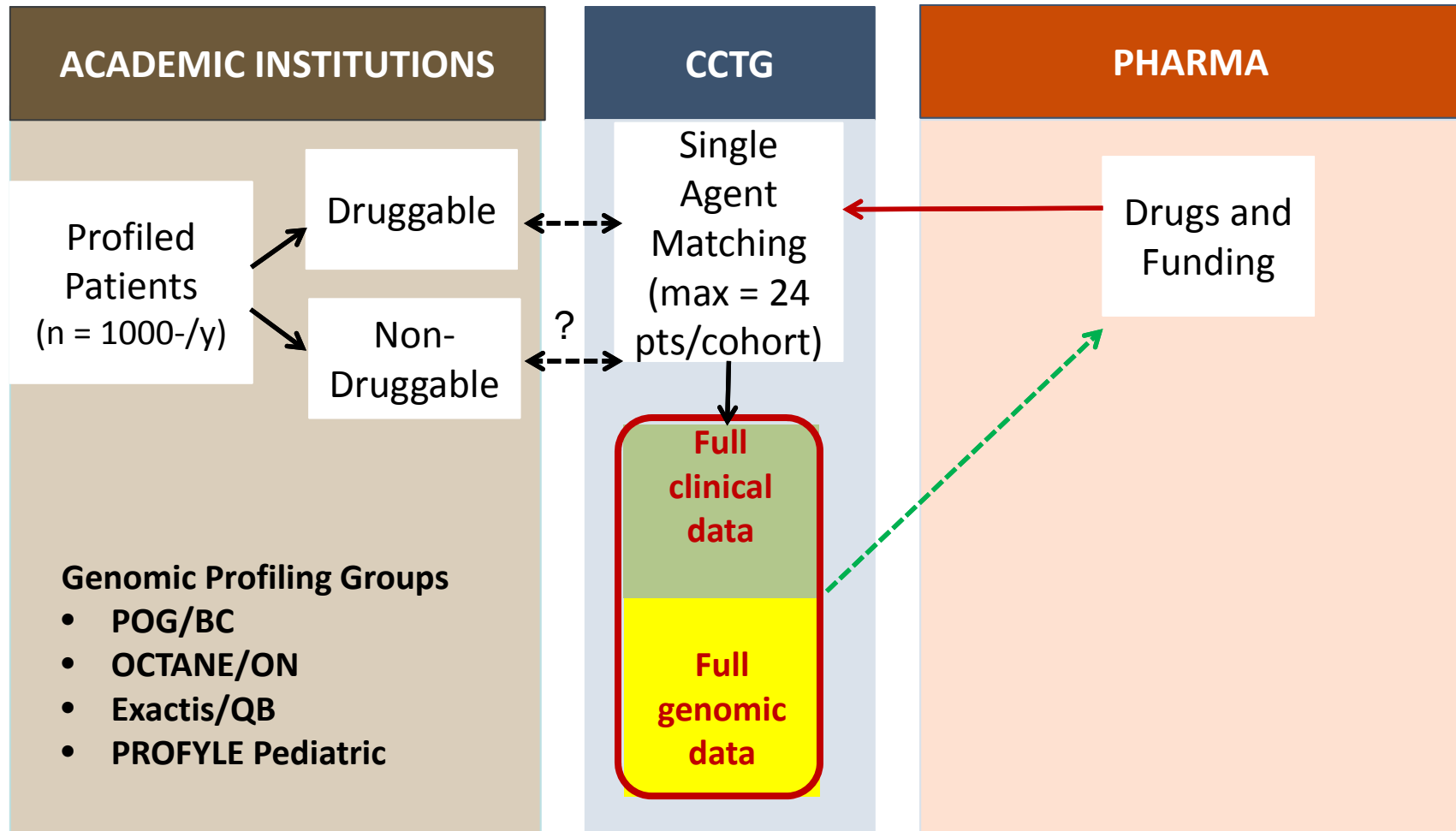
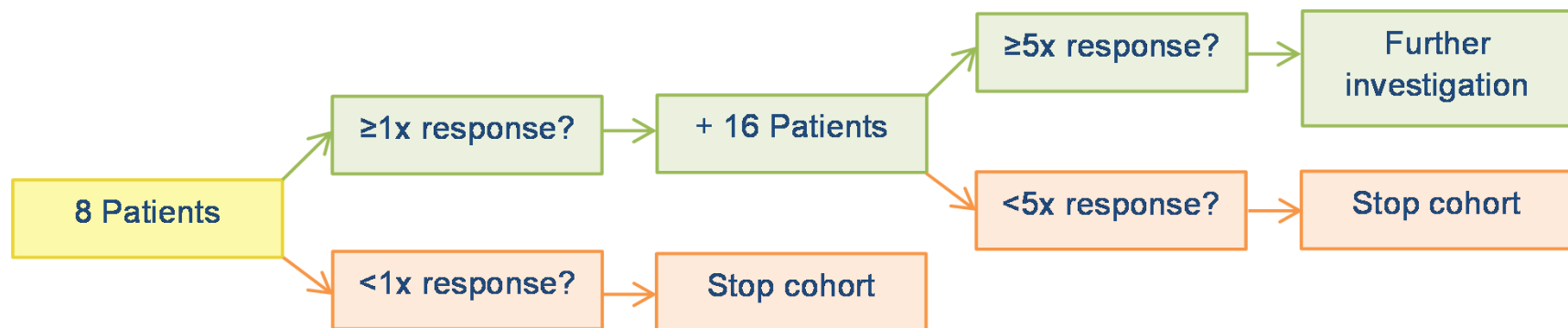Linked with TAPUR and DRUP

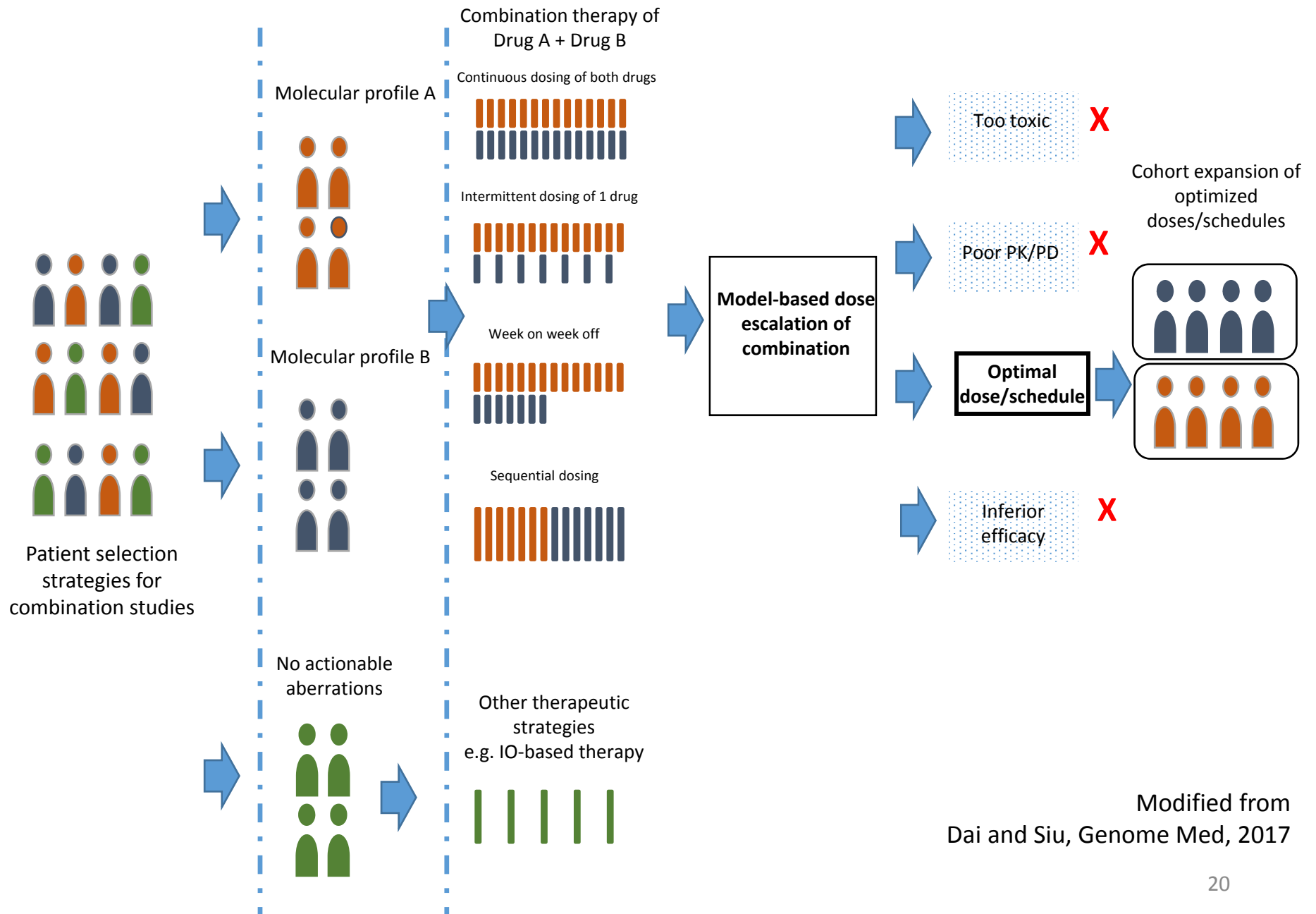☐ Portal   ---> Data transfer   → Drug transfer   ---> Data transfer per agreement

Sample Size Considerations

- Each tumor type, genomic alteration (at the level of the gene and not the specific variant) and matched drug treatment will define a cohort

- The maximum sample size per cohort is 24 patients based on a Simon 2-stage "admissible" design. Each cohort will be designed to have 85% power to reject the null hypothesis of response rate of 10% when the true response rate is 30%

- Because the definition of a cohort may lead to a large number of cohorts, the maximum number of allowable cohorts will be set at 30 and the maximum numbers of patients at 720 patients

Combination Therapies – Adaptive Strategies

Patient selection strategies for combination studies

Molecular profile A

Molecular profile B

No actionable aberrations

Combination therapy of Drug A + Drug B

Continuous dosing of both drugs

Intermittent dosing of 1 drug

Week on week off

Sequential dosing

Other therapeutic strategies e.g. IO-based therapy

Model-based dose escalation of combination

Too toxic X

Poor PK/PD X

Optimal dose/schedule

Inferior efficacy X

Cohort expansion of optimized doses/schedules

Modified from
Dai and Siu, Genome Med, 2017

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TAPUR

Targeted Agent and Profiling Utilization Registry Study

American Society of Clinical Oncology

The Targeted Agent and Profiling Utilization Registry (TAPUR) Study

Principal Investigator: Richard L. Schilsky, M.D., FASCO
Chief Medical Officer, American Society of Clinical Oncology
2318 Mill Road, Suite 800, Alexandria, VA 22314
Phone: (571) 483-1315, Fax: (571) 366-9551
Email: richard.schilsky@asco.org

Overall Goal:

To learn from the real world practice of prescribing targeted therapies to patients with advanced cancer whose tumor harbors a genomic variant known to be a drug target

Figure 4-1: Patient Registration to Enrollment Flowchart in the TAPUR Study
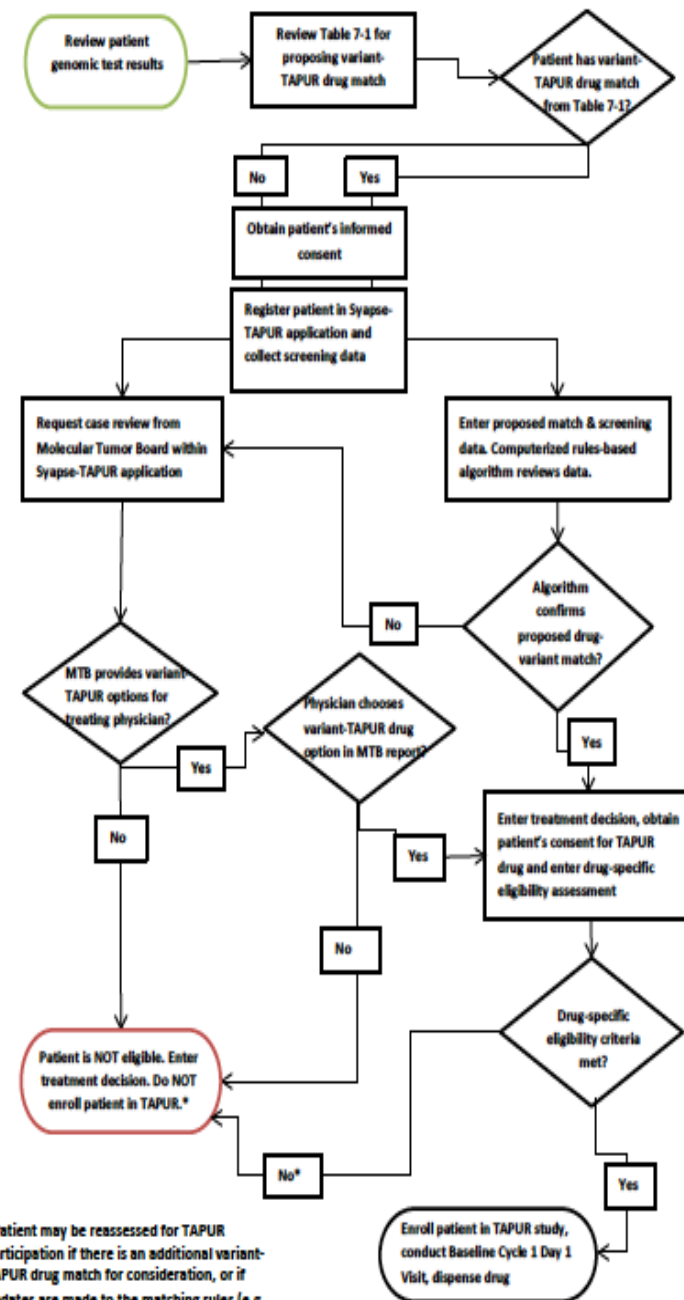
*Patient may be reassessed for TAPUR participation if there is an additional variant-TAPUR drug match for consideration, or if updates are made to the matching rules (e.g. new evidence, additional drugs added to TAPUR).
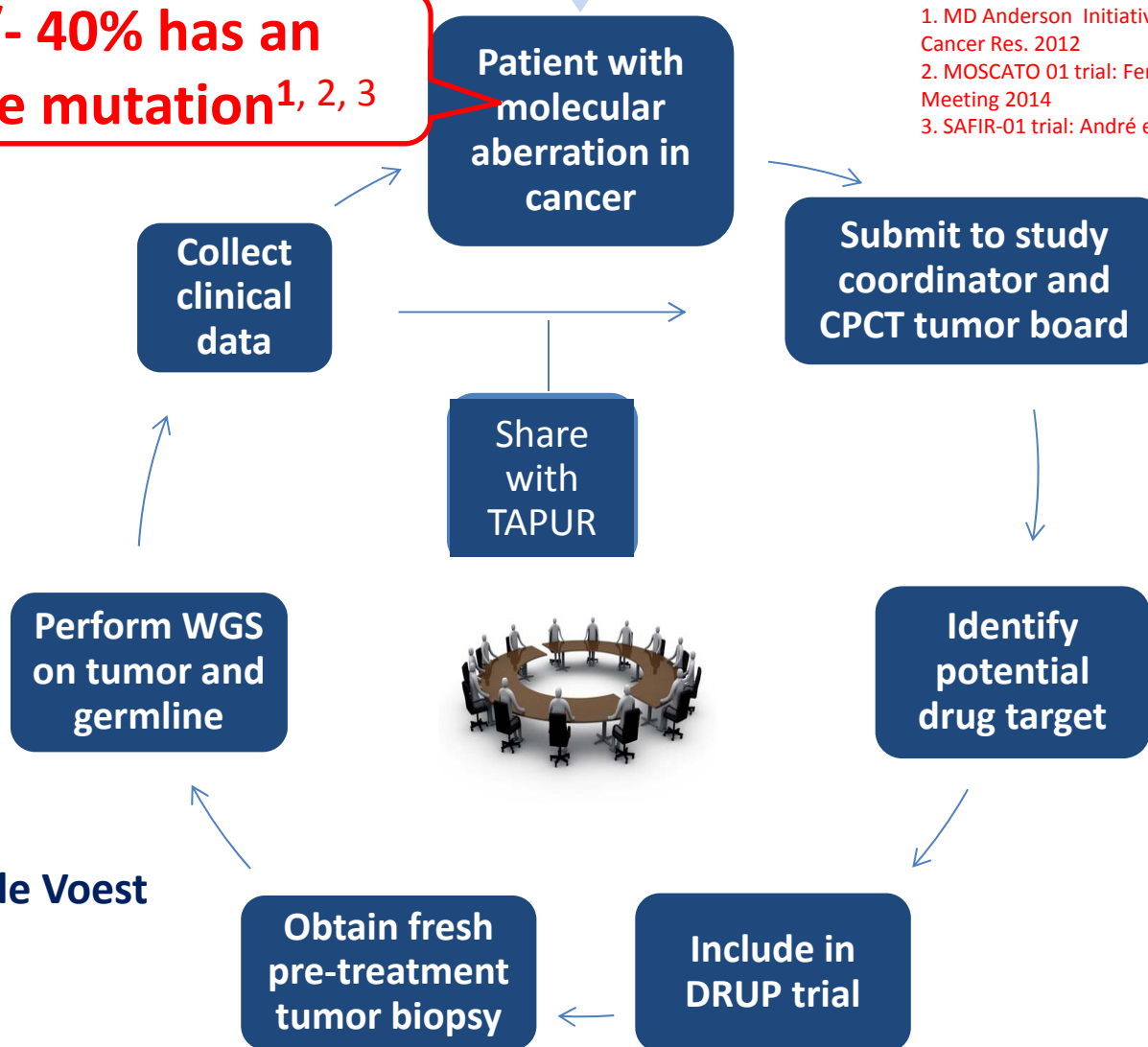
The Drug Rediscovery Protocol (DRUP)

D.L. van der Velden, H.M.W. Verheul, A.J. Gelderblom, E.E. Voest

On behalf of the Centre for Personalized Cancer Treatment

Only +/- 40% has an actionable mutation[1, 2, 3]

1. MD Anderson Initiative: Tsimberidou et al, Clin Cancer Res. 2012
2. MOSCATO 01 trial: Ferté et al., AACR Annual Meeting 2014
3. SAFIR-01 trial: André et al, Lancet Oncol. 2014

Patient with molecular aberration in cancer

Collect clinical data

Submit to study coordinator and CPCT tumor board

Share with TAPUR

Perform WGS on tumor and germline

Identify potential drug target

Courtesy Emile Voest

Obtain fresh pre-treatment tumor biopsy

Include in DRUP trial

Terry Fox Comprehensive Cancer Centre Consortium Network (TF4CN) will incentivize decision-making for IT solutions that align infrastructure and standards

BC Cancer Agency
- Medidata Rave
- cBioPortal
- Quantitative Imaging for Personalized Cancer Medicine
- FlowRepository
- Knowledgebank for Personalized Oncogenomics
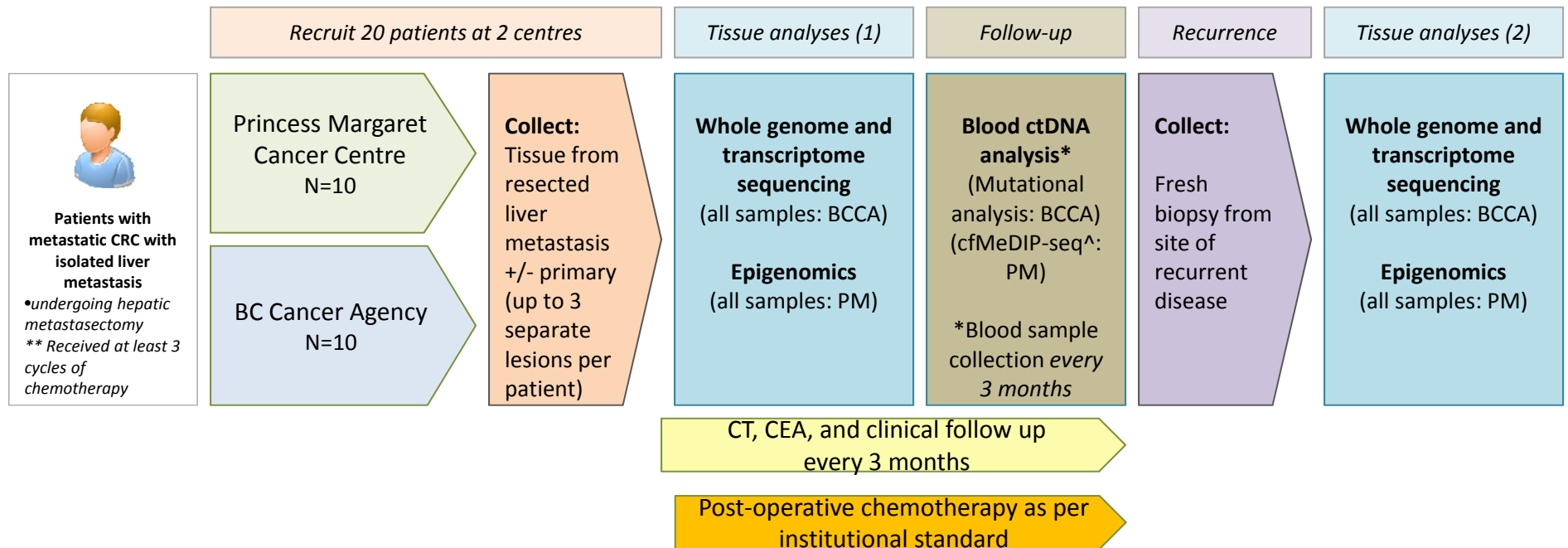- Genome Sciences Centre HPC

Princess Margaret/UHN
- Medidata Rave
- cBioPortal
- Quantitative Imaging for Personalized Cancer Medicine
- RedCap
- Trials App
- CoPath
- Aperio Image Server
- HPC4Health

- ***co-development of common data standards***
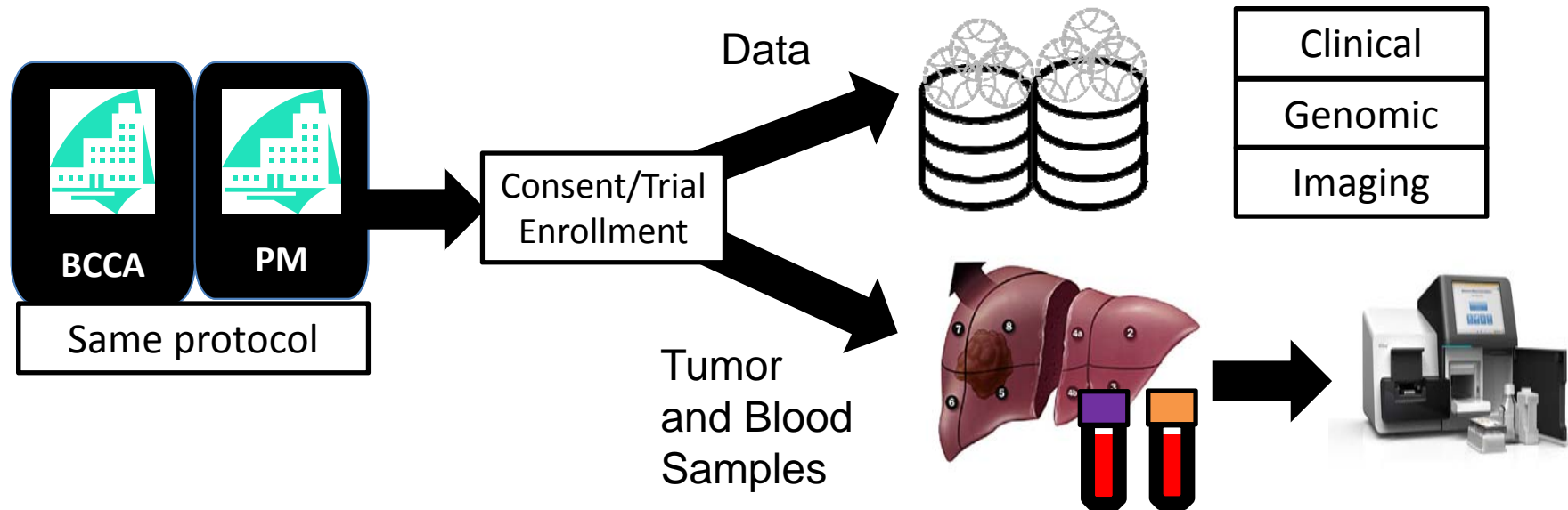- ***harmonization of strategic investments in data systems***

COmprehensive GenoMic Profiling of ColorectalAl CanceR Patients with Isolated Liver MetaStases to Understand RespOnse & ResistaNce to Cancer Therapy
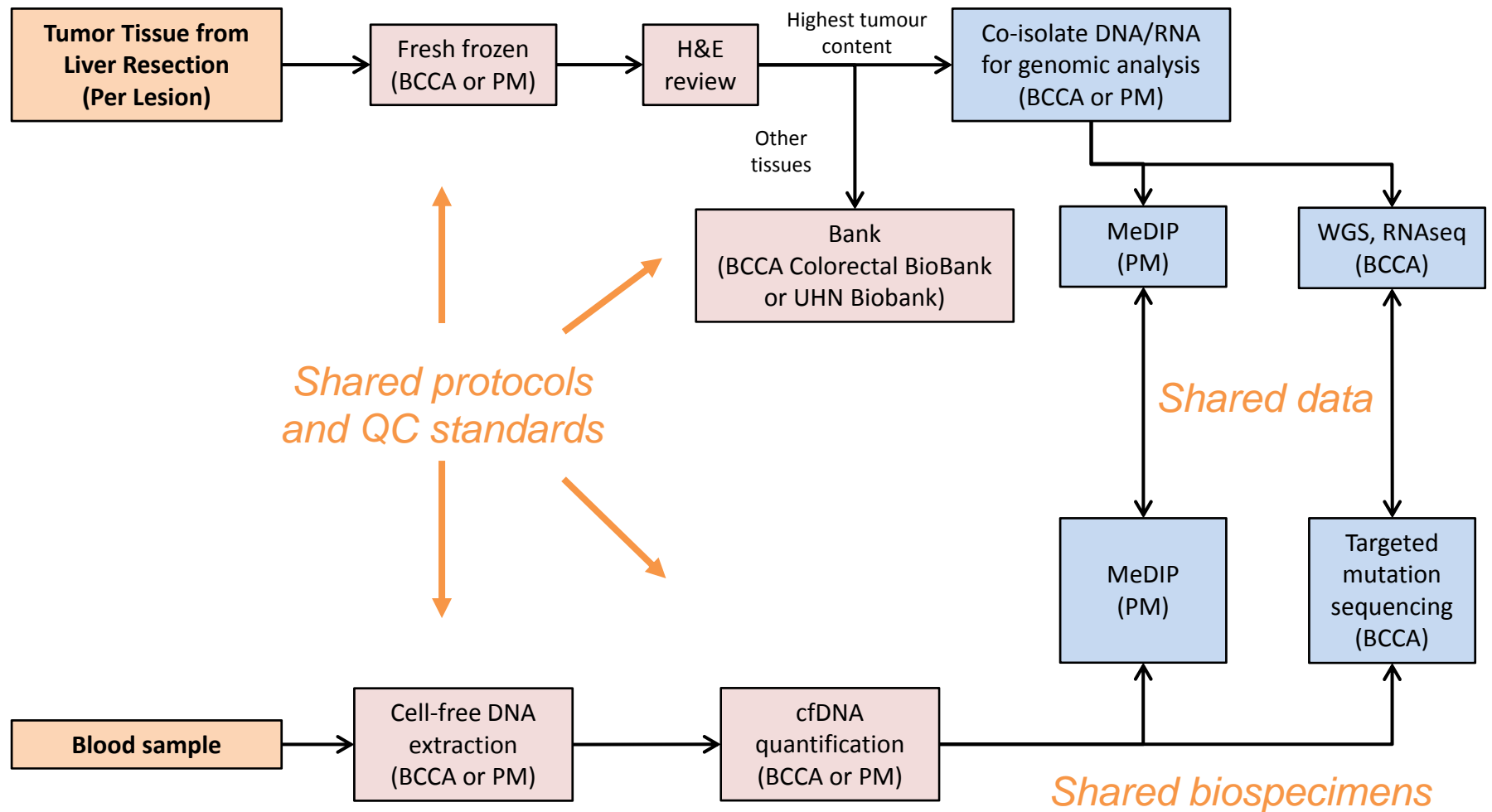## (COMPARISON)
Overall Schema

Patients with metastatic CRC with isolated liver metastasis
- undergoing hepatic metastasectomy
** Received at least 3 cycles of chemotherapy

Recruit 20 patients at 2 centres	Tissue analyses (1)	Follow-up	Recurrence	Tissue analyses (2)

Princess Margaret Cancer Centre N=10

BC Cancer Agency N=10

Collect: Tissue from resected liver metastasis +/- primary (up to 3 separate lesions per patient)

Whole genome and transcriptome sequencing (all samples: BCCA)

Epigenomics (all samples: PM)

Blood ctDNA analysis* (Mutational analysis: BCCA) (cfMeDIP-seq^: PM)

*Blood sample collection *every 3 months*

Collect: Fresh biopsy from site of recurrent disease

Whole genome and transcriptome sequencing (all samples: BCCA)

Epigenomics (all samples: PM)

CT, CEA, and clinical follow up every 3 months

Post-operative chemotherapy as per institutional standard

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COMPARSION:
Project Management and Interaction of Team Members
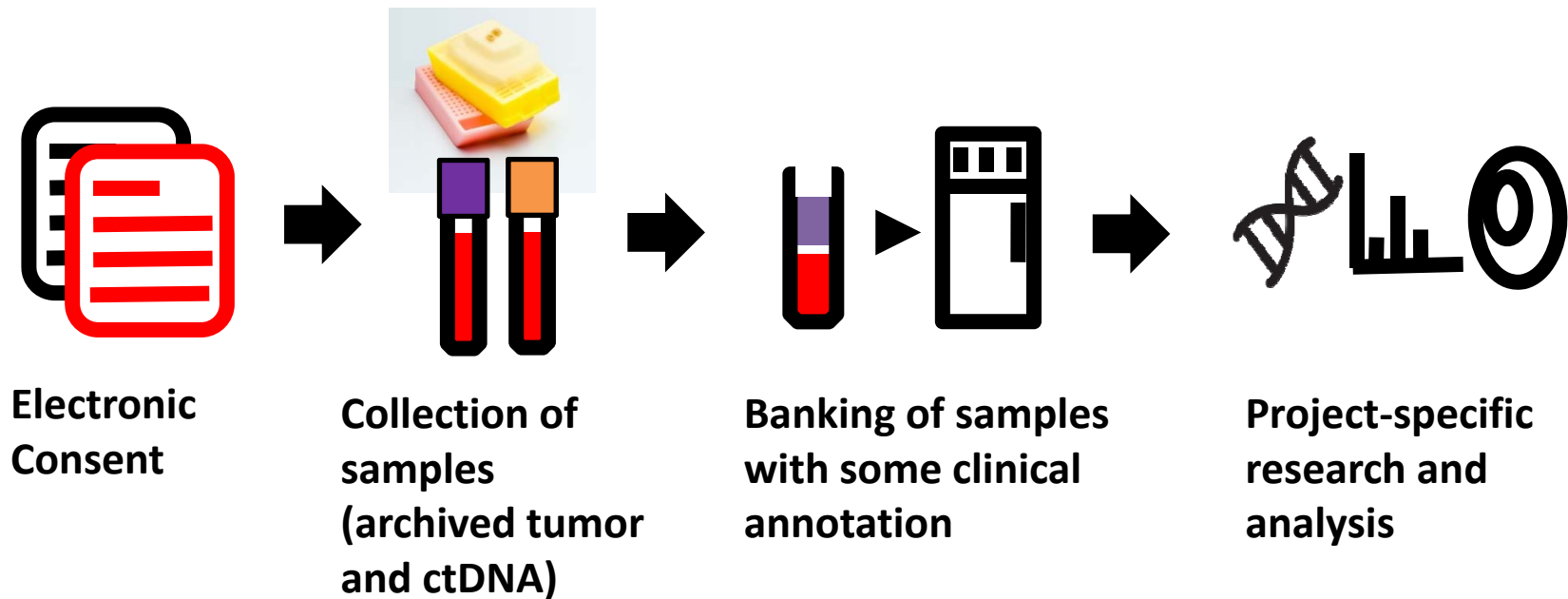

Documents to Share	Website Databases to Share
Clinical Trial Protocol and Informed Consent Forms	SharePoint, Lab Key, AeroFS
Nucleic Acid Extraction, Sample Processing and Shipment SOPs (tumor, cfDNA)	Genomic Data Deposition (cBioPortal)
Data Submission SOPs	Imaging Portal

COMPARISON:
Biospecimen Workflow, Protocols, and Data Sharing

LIquid Biopsy Evaluation and Repository Development AT PrincEss Margaret
(LIBERATE)

Electronic Consent → **Collection of samples (archived tumor and ctDNA)** → **Banking of samples with some clinical annotation** → **Project-specific research and analysis**
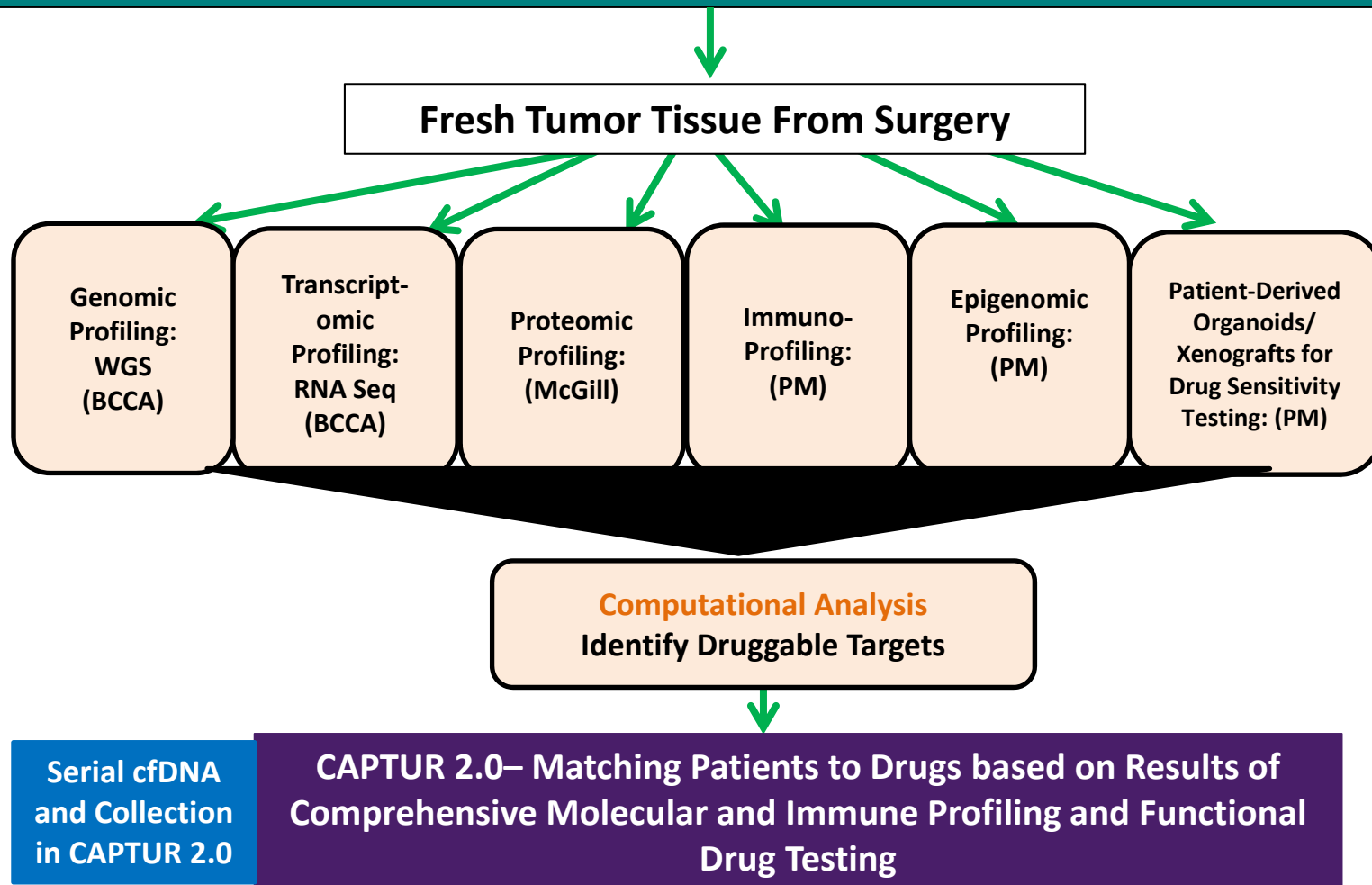
- 5-Year Plan: 250-500-750-1000-1500 (= 4000 patients)
- Creating the framework and infrastructure accessible to all Princess Margaret investigators and researchers
- Plan to open in May 2017 with ~6 pilot projects to start

Rama Khokha, Philippe Bedard, Trevor Pugh, Daniel De Carvalho, Scott Bratman, Kathy Han, Hal Berman, Dianne Chadwick, David Cescon, Raymond Kim, Christine Elser, Geoffrey Liu, Amit Oza, Lillian Siu

Research Group	Principal Investigator(s)
Early detection of cancer in high-risk patients through routine profiling of circulating tumour DNA	Dr. Trevor Pugh Dr. Christine Elser Dr. Raymond Kim
Multiple Myeloma (MM)	Dr. Suzanne Trudel Dr. Trevor Pugh
Leveraging Vulnerabilities in Macromolecular Homeostasis as Therapeutic Targets in Ovarian Cancer (Ovarian TRI)	Dr. Amit Oza Dr. Robert Rottapel
Comprehensive Genomic Profiling of Colorectal Cancer Patients with Isolated Liver Metastases to Understand Response & Resistance to Cancer Therapy (COMPARISON)	Dr. Lillian Siu Dr. Kyaw Aung
ctDNA evaluation in early breast cancer (TRACER)	Dr. David Cescon
FDG-PET and Circulating HPV in Patients with Cervical Cancer Treated with Definitive Chemoradiation	Dr. Scott Bratman Dr. Kathy Han

Comprehensive Precision Oncology Program for Patients with Oligometastatic Disease at High Risk of Recurrence (PrOPPOR): CCTG, PM, BCCA, McGill

Cancer Patients with Oligometastases (Single Metastasis) Undergoing Surgical Resection

Fresh Tumor Tissue From Surgery

| Genomic Profiling: WGS (BCCA) | Transcript-omic Profiling: RNA Seq (BCCA) | Proteomic Profiling: (McGill) | Immuno-Profiling: (PM) | Epigenomic Profiling: (PM) | Patient-Derived Organoids/Xenografts for Drug Sensitivity Testing: (PM) |

Computational Analysis
Identify Druggable Targets

Serial cfDNA and Collection in CAPTUR 2.0

CAPTUR 2.0– Matching Patients to Drugs based on Results of Comprehensive Molecular and Immune Profiling and Functional Drug Testing

Socio-Economic Benefit: 1) Pan-Canadian Scientific Collaborations. 2) Identification of Novel Therapeutic Targets. 3) Increase Actionability for Patients with No-Evidence of Disease (NED) but at Risk of Relapse. 4) Potential Curative Intervention for High Risk Patients. 5) Monitoring of Resistance.

Conclusions

- Next generation sequencing and other molecular profiling strategies are increasingly feasible and affordable

- The translation of molecular profiling results to clinical action remains challenging, despite the rapid emergence of genomic-based trials of approved and/or investigational agents

- Need to move beyond single agent to combination therapies – but there are biological, logistical and design complexities

- Functional genomics, transcriptomics etc may increase actionability

- "Collective wisdom" with responsive and effective data sharing is critical for rapid learning

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Applied Cancer Research Units Grant