Translating cancer genomes into personalized health and disease management

Tom Hudson

Ontario Institute for Cancer Research

Cancer statistics

World (2008)	6,629,112 New cases	4,225,662 Deaths
USA (2010)	1,529,560 New cases	562,875 Deaths
Canada (2010)	173,800 New cases	76,200 Deaths

- 40% of Canadian women and 45% of men will develop cancer during their lifetimes.
- 1 out of every 4 Canadians are expected to die from cancer.
- Cancer is the leading cause of premature death in Canada. This represents 32% of the potential years of life lost resulting from all causes of death.

Source: GLOBOCAN 2008/IARC; American Cancer Society; Canadian Cancer Society.

Promises of cancer genome research to patients, health care providers and payers

- **Genetic information will be used to predict risk, optimize screening programs, identify tumours at early stages when disease is more often curable, save health care costs;**
- **Cancer diagnosis will be more precise, will provide more accurate prognostic information and allow optimization of treatment interventions;**
- **New therapies will be developed that target specific alterations in cancer cells, reducing the need for highly toxic chemotherapies.**

Current status: A few successes – potential far from being realized

Outline

- Genome technologies
- Inherited genomic variation and cancer
  - Genetic predisposition to colon cancer
- Acquired (somatic) variation and cancer
  - Pancreatic Cancer Genome Project
- Concepts of personalized medicine
  - Implementation by the Ontario Institute for Cancer Research

Sequencing Evolution

~ 20 years

<1,000 bases per day

>10,000 bases per day

- >1,000,000 bases per day

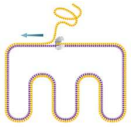
- >200,000,000 bases per day

Human Genome Project

Sequencing Revolution

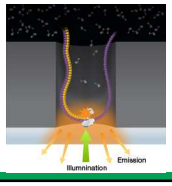
Pacific Biosciences RS

Single molecule, Simple sample prep
Long reads (>10kb)



2010: ~50 Mb, 0.5 hour, $99

~2015; Complete genomes, 15 minutes, < $1000

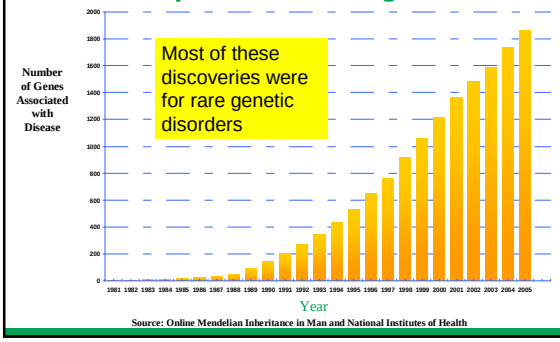


Sequencing adapted to study DNA, RNA, methylation and chromatin

- SNP/indel discovery
  - Targeted genomic sequencing: exome
- Structural variation
  - Rearrangements,large indel, copy number
- Whole transcriptome sequencing
  - mRNA and miRNA
- Copy number variation
  - Sequence, Microarray and Beadstation
- Small RNA discovery/sequencing
- Whole genome sequencing
- Epigenomics
  - Chromatin IP transcription factor binding (ChIP-seq)
  - Methylation/Methylome

Blood and Tissues

Cumulative pace of disease gene discovery



Human Genome: 3 billion bases

ATGCCGATCGTACGACACATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCATCGTACT
TACTGACTGCATCGTACTGACTGCACATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCC
CATCGTACTGACTGTCTAGTCTAAACACATCCCACATATCGTCATCGTACTGACTGTCTAGTCTA
CATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCTATGCCGATCGTACGACACATATCG
ACTGTCTAGTCTAAACACATCCATCGTACTGAC CTGCA
TCGTACTGACTGTCTAGTCTAAACACATCCGAC TAAA
CACATCCCACTTTACCCATATATCGTCATCGTA ATAT
CGTCATCGTACTGACTGTCTAGTCTAAACACAT GTCAT
CGTACTGCCCTACGGGACTGTCTAGTCTAAAC GACT
GCATCGTACTGACTGCACATATCGTCATACATAGACTTCGTACTGACTGTCTAGTCTAAACACCC
CACATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCCACTTTACCCATGCATCGTACTG
ACTGTCTAGTCTAAACACATCCCACATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCC
AGCATCCATCCATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCTATGCCGATCGTACG
ACACATATCGTCATCGTACTGCCCTACGGGACTGTCTAGTCTAAACACATCCATCGTACTGACG
CATCGTACTGACTGCATCGTACTGACTGCACATATCGTCATACATAGACTTCGTACTGACTGTCT
AGTCTAAACACATCCCACATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCCACTTTAC
CCATGATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCACATATCGTCATCGTACTGA
CTGTCTAGTCTAAACACATCCTATACATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCT
AT AGACT
CG AAAC
AC ATAT
CGTCATCGTACTGACTGTCTAGTCTAAACACATCCTATAGCCGATCGTACGACACATATCGTCA
CGTACTGCCCTACGGGACTGTCTAGTCTAAACACATCCATCGTACTGACTGCATCGTACGCCGA

Polymorphisms

~ 15 million polymorphisms in the human genome with a frequency > 1%

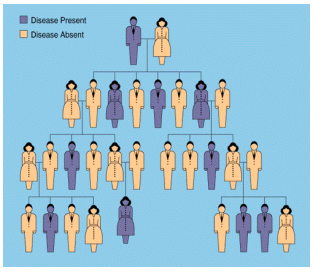
International HapMap Project

- Describe the common patterns of sequence variation in the human genome
- Include multiple populations with ancestry from parts of Africa, Asia and Europe
- Make this information freely available in the public domain
- Provide tools to aid discovery of genetic variants that affect common disease in association studies.

Gene discoveries for common complex diseases

Genes identified before 2005 (Pre-HapMap)	Loci identified since 2005 (HapMap and GWAS)
•Breast Cancer Genes	•Macular Degeneration
•Alzheimer's Disease	•Type 2 Diabetes
•**Colon Cancer**	•Prostate Cancer
	•Lupus
	•Myocardial Infarction
	•Inflammatory Bowel Disease
	•**Colon Cancer**
	> 2000 other loci!

1995: HNPCC mutations were identified in families with very high rates of colon cancer



They cause about 90 percent of all inherited colon cancers, or about 15 percent of colon cancers.

Testing is available for individuals with family history

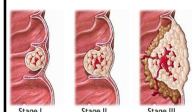
THE ARCTIC PROJECT
Assessment of Risk of Colorectal Tumors in Canada

Design:

- 1200 Cases (Ontario)
- 1200 Controls (Ontario)
- 1.4 billion genetic tests

Output:

- Predictors of Disease
- Disease prevention
- ARCTIC kits



Brent Zanke, Steve Gallinger, Celia Greenwood, Michele Cotterchio, Tom Hudson

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nature genetics

Genome-wide association scan identifies a colorectal cancer susceptibility locus on chromosome 8q24

Brent W Zanke[1–3], Celia MT Greenwood[1,4,5], Jagadish Rangrej[4], Rafal Kustra[1,5], Albert Tenesa[6], Susan M Farrington[6], James Prendergast[6], Sylviane Olschwang[7], Theodore Chiang[4], Edgar Crowdy[4], Vincent Ferretti[8], Philippe Laflamme[8], Saravanan Sundararajan[8], Stéphanie Roumy[8], Jean-François Olivier[8], Frédérick Robidoux[8], Robert Sladek[8], Alexandre Montpetit[8], Peter Campbell[9], Stephane Bezieau[10], Anne Marie O'Shea[9], George Zogopoulos[9], Michelle Cotterchio[1,5], Polly Newcomb[11], John McLaughlin[1,9], Ban Younghusband[12], Roger Green[12], Jane Green[12], Mary E M Porteous[13], Harry Campbell[6,14], Helene Blanche[15], Mourad Sahbatou[15], Emmanuel Tubacher[15], Catherine Bonaiti-Pellié[16], Bruno Buecher[10], Elio Riboli[17], Sebastien Kury[10], Stephen J Chanock[18], John Potter[11], Gilles Thomas[19], Steven Gallinger[1,9], Thomas J Hudson[2,8] & Malcolm G Dunlop[6]

Nat Genet. 2007 Aug;39(8):989-94. Epub 2007 Jul 8.

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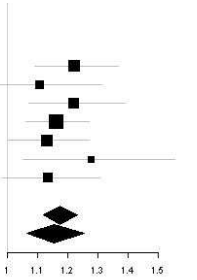
rs10505477 (8q24 locus)

First genetic marker validated in > 10,000 subjects

Population	OR	SE
Ontario	1.22	0.058
Seattle/Newfoundland	1.11	0.087
Scotland3	1.22	0.066
Scotland4	1.16	0.046
France/Nantes	1.13	0.060
France/Familial	1.28	0.099
EPIC	1.13	0.072
Summary-All	**1.17**	**0.024**
French/EPIC only	**1.16**	**0.042**



Odds ratios for log-additive model

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Published GWAS for CRC with n>10,000

- **Zanke *et al, Nat Genet*, 2007**
- **Tomlinson *et al, Nat Genet*, 2007**
- **Broderick *et al, Nat Genet*, 2007**
- **Jaeger *et al, Nat Genet*, 2008**
- **Tenesa *et al, Nat Genet*, 2008**
- **Tomlinson *et al, Nat Genet*, 2008**
- **Houlston *et al, Nat Genet*, 2008**

- 10 validated loci
- ORs: 1.10 to 1.25
- Gene identified:

  SMAD7
- Nearby genes
  - BMP2
  - BMP4
  - Cadhedrin 1
  - Gremlin1

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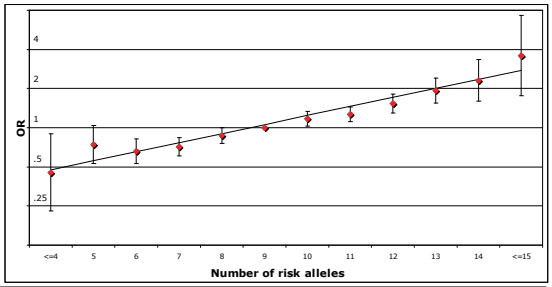
Risk versus CRC-allele Count

Houlston *et al, Nat Genet*, 2008



Cases	**<1%**	**1%**	**3%**	**7%**	**14%**	**19%**	**20%**	**17%**	**11%**	**5%**	**2%**	**<1%**
Controls	**<1%**	**2%**	**5%**	**11%**	**17%**	**20%**	**18%**	**14%**	**7%**	**3%**	**1%**	**<1%**

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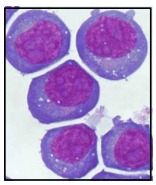
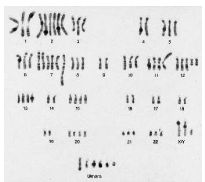
Cancer
A disease of the genome





Lessons learned from cancer genome research:

- **Heterogeneity within and across tumour types;**
- **High rate of abnormalities (driver vs. passenger);**
- **Sample quality matters.**

Challenge in treating cancer:

- **Every tumour is different;**
- **Every cancer patient is different.**

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International Cancer Genomics Strategy Meeting

October 1–2, 2007 Toronto (Canada)

22 countries represented

120 participants

- 34 genome or cancer centre directors;
- 24 representatives from funding agencies;
- 62 scientists selected to represent ethics, technologies, statistics, informatics, pathology, clinical oncology and cancer biology.

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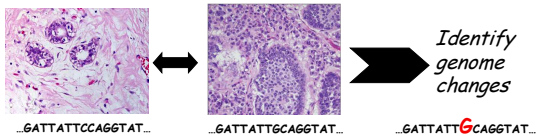
International Cancer Genome Consortium

- Collect ~500 tumour/normal pairs from each of 50 different major cancer types;
- Comprehensive genome analysis of each pair: genome, transcriptome & methylome;
- Make the data available to the research community & public.



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Rationale for an international consortium

- The **scope is huge**, such that no country can do it all;
- Coordinated cancer genome initiatives will **reduce duplication of effort** for common tumours and ensure complete studies for many less frequent forms of cancer;
- **Standardization and uniform quality measures** across studies will enable the **merging of datasets, increasing power** to detect additional targets;
- The **spectrum of many cancers varies across the world** for many tumour types;
- The ICGC will **accelerate the dissemination of genomic and analytical methods** across participating sites and the user community.

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Vol 464|15 April 2010|doi:10.1038/nature08987 nature

PERSPECTIVES

International network of cancer genome projects

The International Cancer Genome Consortium*

The International Cancer Genome Consortium (ICGC) was launched to coordinate large-scale cancer genome studies in tumours from 50 different cancer types and/or subtypes that are of clinical and societal importance across the globe. Systematic studies of more than 25,000 cancer genomes at the genomic, epigenomic and transcriptomic levels will reveal the repertoire of oncogenic mutations, uncover traces of the mutagenic influences, define clinically relevant subtypes for prognosis and therapeutic management, and enable the development of new cancer therapies.

Nature 464, 993-998 (15 April 2010)

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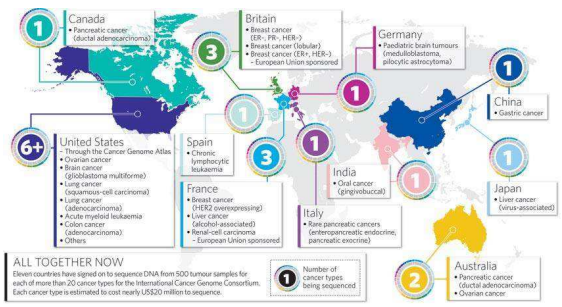
ICGC Partners: 12 countries, 38 projects

Commitments for > 10,000 cancer genomes



Heidi Ledford, Nature, 2010

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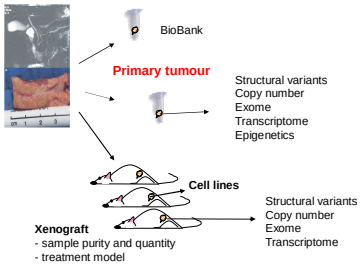
Pancreatic tumour sequencing at OICR

Sample collection: ~75/year

Blood: germline DNA



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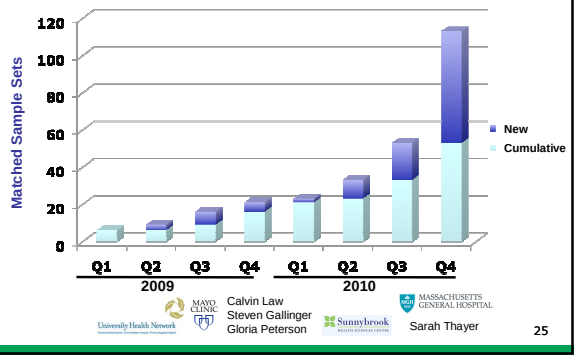
Pancreatic sample acquisition (2009-10)



Calvin Law
Steven Gallinger
Gloria Peterson
Sarah Thayer

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OICR Cancer Genomics Platform: ~5,000 Gb/mo (1500 raw genomes)

7 GAIIx

3 HiSeq 2000

5 SOLiDv3/4

1 Pacific Biosciences RS

ACGT…

3 PB storage
3,600 cores

2 pancreatic CA samples in DCC
5 nearing submission

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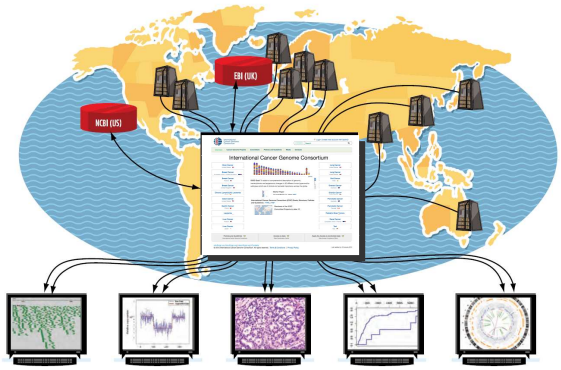
ICGC data is distributed, but is accessible through a common portal



Submissions to DCC as of September 2010

- Cancer types: 8 (from 8 centres, including TCGA)
- Donors: 1,474
  - Simple somatic mutations: 107,478
  - Copy number mutations: 23,302
  - Structural rearrangements: 4,562
  - Genes affected by simple somatic mutations: 18,201
  - Genes affected by copy number mutations: 12,407
  - Genes affected by structural rearrangements: 815
- *Only open tier data currently available*

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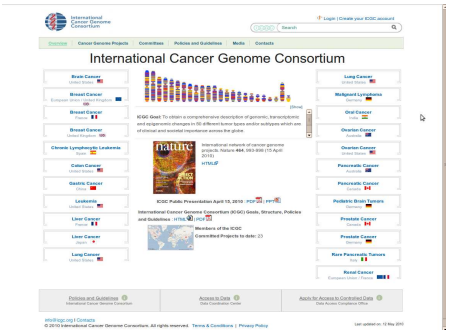
ICGC web portal



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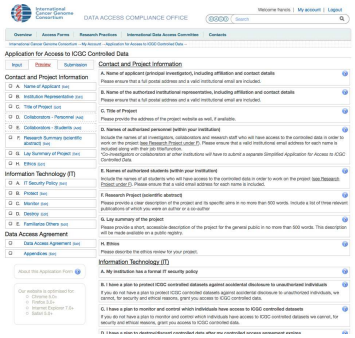
DACO Application Form



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What is personalized medicine?

"It's no longer one size fits all. Your therapy may be different from mine, even though we have the same disease, because of differences in genetic makeup, lifestyle, health history and other factors".

Diana Bartlett, Keck Graduate Institute

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Definitions

Personalized Medicine (NCI): A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose and treat disease.

Biomarker (NIH): A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Biological **Target** (Wiki): A protein or nucleic acid (DNA or RNA) whose activity can be modified by an external stimulus.

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Personalized medicine has started

Examples of validated diagnostic tests that can be used to select cancer therapies

Her2 test for breast cancer	**Herceptin**
Oncotype DX	**Adjuvant chemotherapy for breast cancer**
K-RAS mutations	**EGFR inhibitors for colon cancer**
Many more coming...	***Many more coming...***

Challenges and Opportunities

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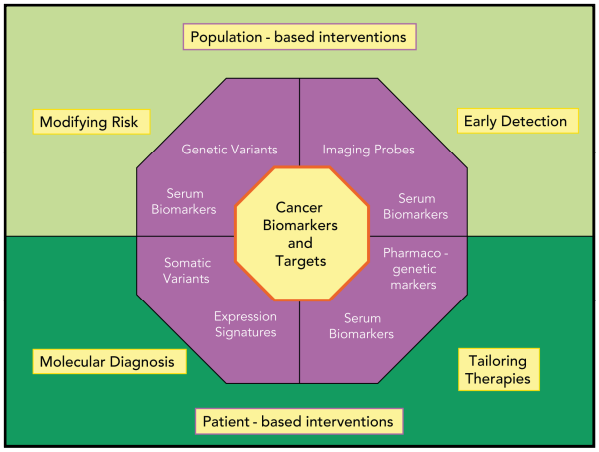

Translating cancer genomes into personalized health and disease management at the Ontario Institute for Cancer Research

- Develop translation paths from discovery to impact cancer (reduce incidence, morbidity and mortality);
- Prioritize resources on problems that matter most to clinicians
- Develop partnerships in Ontario, Canada and internationally.

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The Canadian Partnership for Tomorrow Project

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Goals

- to enrol **300,000** Canadians aged 35-69 years into a cohort study (‘**population laboratory**‘)
- to follow cohort participants for **up to 50 years**, periodically collecting health related information and biological samples
- to build up layers of information and biological samples over time, eventually leading to in-depth study of why some people in the cohort develop cancer, or other chronic diseases, and others do not

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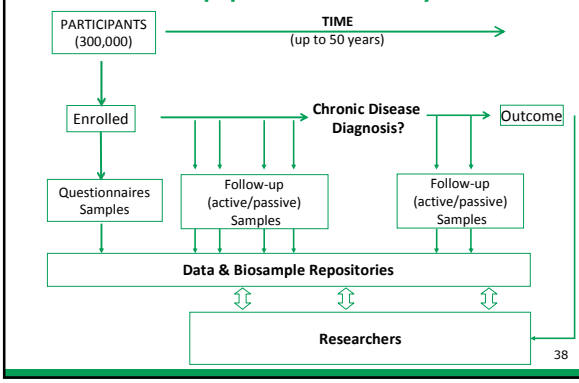
CPTP:
A population laboratory



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Federated model

Cohorts
Alberta (The Tomorrow Project)
Atlantic Canada (Partnership for Tomorrow’s Health)
British Columbia (BC Generations Project)
Ontario (Ontario Health Study)
Quebec (CARTaGENE)

National coordinating centre

Task Forces & Working groups
ELSI and Privacy TF
Information Technology TF
Harmonization TF
Environment & Occupation Advisory Group
Physical measures working group
Biological samples working group

Canadian Partnership for Tomorrow Project

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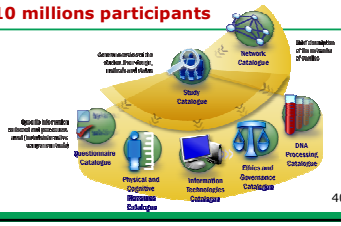
Power enhanced by P3G

P³G OBSERVATORY (www.p3gobservatory.org)

159 large population-based studies
(>10 000 healthy participants)
(P³G members and non-members)

Over 10 millions participants



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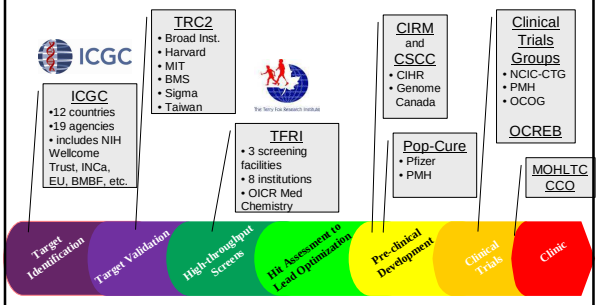
OICR partnerships in the target-to-drug pipeline



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Adoption of more Personalized Medicine for Cancer

OICR/PMH Initiative

Introduction of genomic testing into clinical trials and ultimately into clinical practice

Collaboration with other provincial initiatives

MOHLTC
• develop policy for pharmacogenetics testing

CCO
• develop guidelines for implementation of pharmacogenetics tests

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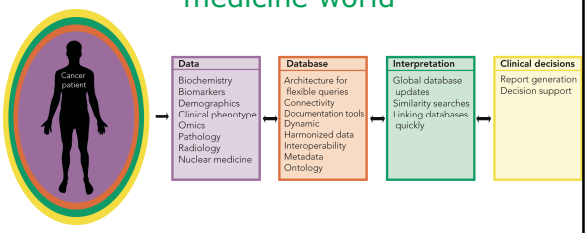
Ontario Institute for Cancer Research
science → discoveries → solutions

Digital environment needed to support clinical decisions in a personalized medicine world

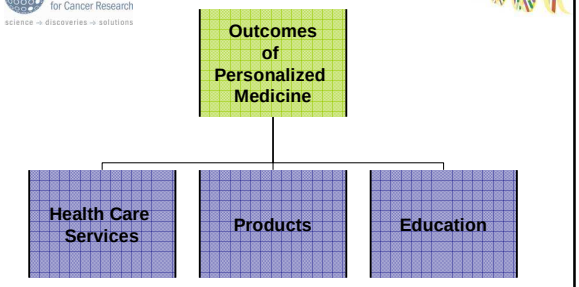


Ontario Institute for Cancer Research
science → discoveries → solutions

Requirements for personalized medicine in canada

- Maintain leadership in fundamental sciences that lead to better understanding of the molecular basis of disease;
- Establish translational research programs that have clinical end-points that address important clinical problems;
- Support translational research platforms such as cohorts, clinical trials, that can validate biomarkers, imaging probes and targeted agents as tools for clinical management;
- Support health services research via linked-databases;
- Develop partnerships between academia, health care providers, regulatory agencies, and industry.

Ontario Institute for Cancer Research
science → discoveries → solutions



More effective and safer therapies, increased survival, improved quality of life, stronger economy.

Ontario Institute for Cancer Research
science → discoveries → solutions

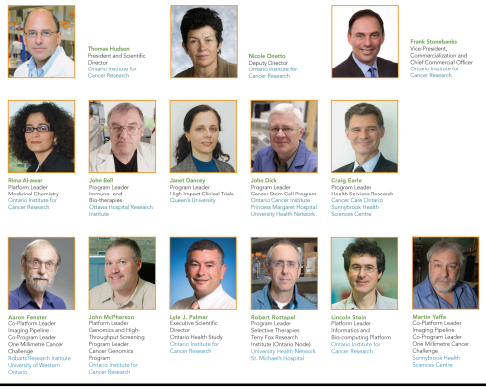
International Cancer Genome Consortium

Madrid, Spain – March 2010

ICGC

Ontario Institute for Cancer Research
science → discoveries → solutions

OICR Leaders



Ontario Institute for Cancer Research
science → discoveries → solutions

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Ontario

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CIHR IRSC

Canadian Cancer Society | Société canadienne du cancer

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ENGAGE