

Building the Canadian Cancer Study within the Canadian Partnership for Tomorrow's Health (CanPath)

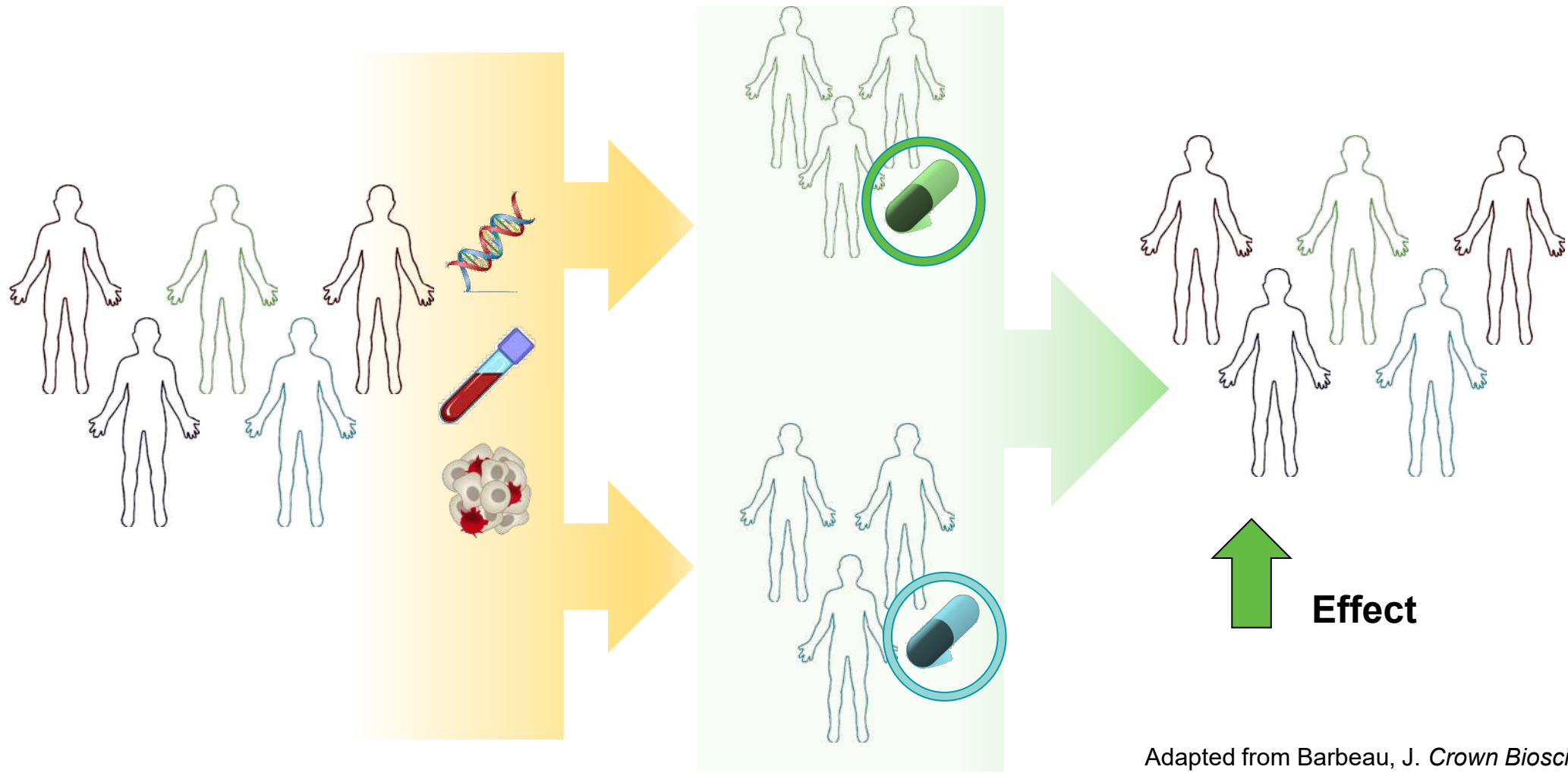
Kimberly Skead

PhD Candidate, Dept. of Molecular Genetics, University of Toronto & the Ontario Institute for Cancer Research

National Scientific Coordinator, CanPath

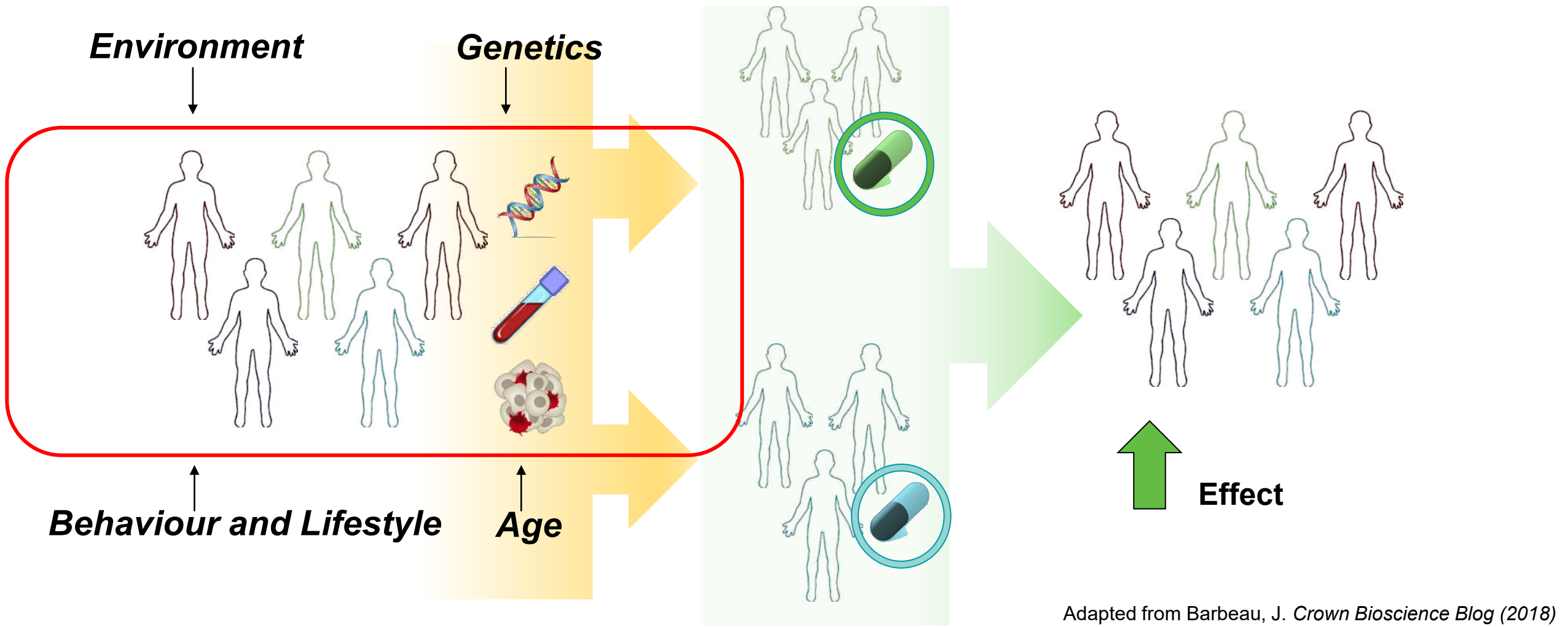


Personalized approaches to improving health outcomes



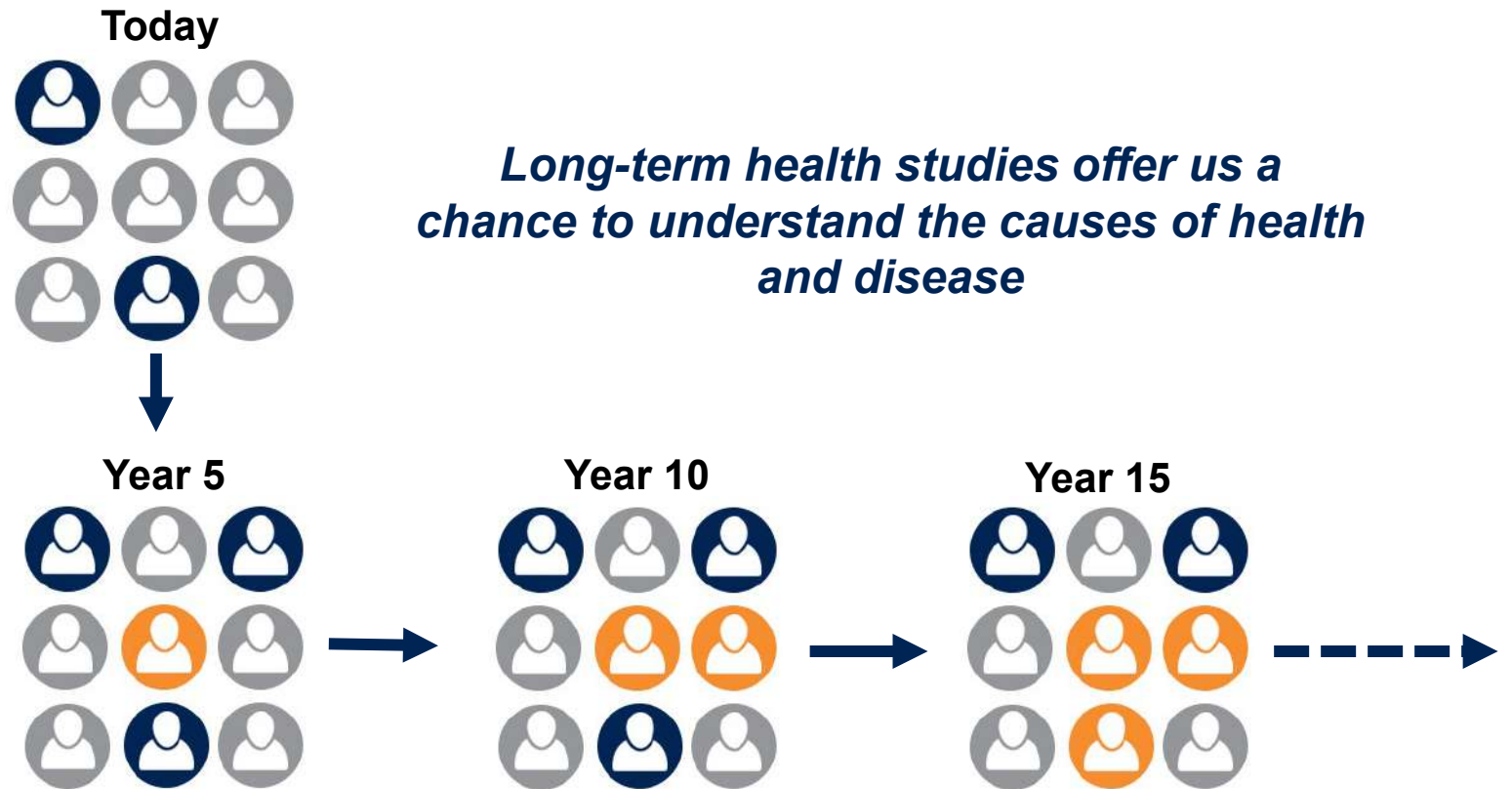
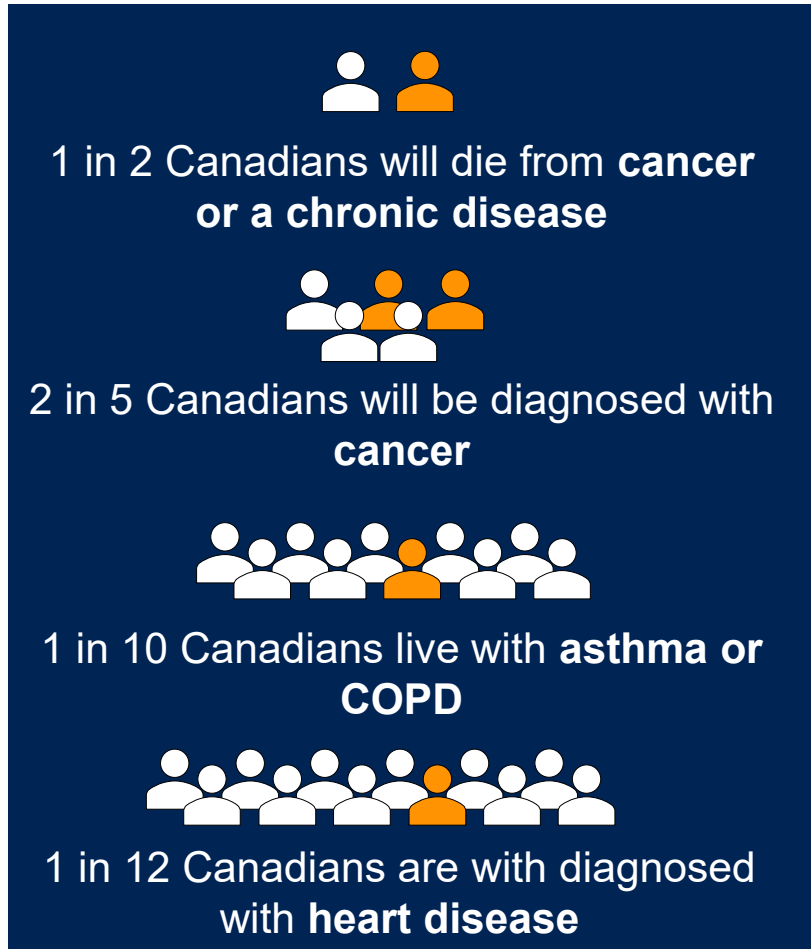
Adapted from Barbeau, J. *Crown Bioscience Blog* (2018)

Personalized approaches to improving health outcomes



Adapted from Barbeau, J. *Crown Bioscience Blog* (2018)

Rising levels of chronic disease are one of Canada's largest public health challenges



[*Manolio et al, Nature Reviews Genetics 2006 \(re: value of prospective cohorts\).](#)

Many countries have been investing in building large population cohorts

For Canada to be competitive in health research, it is crucial to have a large population cohort.

CanPath is
working with other
large cohorts around the world
through IHCC
(International Hundred
Thousand Cohort Consortium)



International 100K Cohort Consortium

Canadian Partnership for Tomorrow's Health (CanPath)

23andMe
Biobank Japan
China Kadoorie Biobank
EPIC
Kaiser Permanente Research Program
LifeGene
Million Veteran Program
Million Women Study
Multiethnic Cohort Study
MyCode Community Health Initiative
Nurses' Health Study (NHS/NHSII)
US Precision Medicine Initiative/All of Us
Tohoku Medical Megabank Project
UK Biobank



The Canadian Cancer Study within the Canadian Partnership for Tomorrow's Health

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An overview of the
Canadian Partnership for
Tomorrow's Health

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Mapping cancer cases in
CanPath with linkages

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Mapping cancer cases in
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Using CanPath to identify
the earliest events in
cancer evolution

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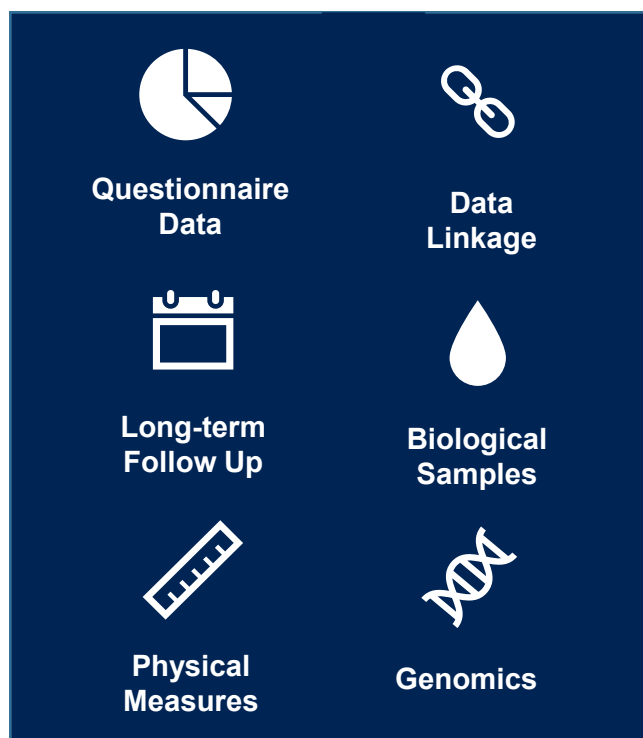
Mapping cancer cases in
CanPath with linkages



Using CanPath to identify
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CanPath is following the health of 330,000 adult Canadians for decades

CanPath is a population-health research platform built to assess the effect of genetics, behavior, health history and environment on chronic diseases.



CanPath has been supporting Canadian research since 2008

Launch of the Healthy Future Sask Research Project

CPTP becomes CanPath & first follow-up data released

COVID-19 data released

Recruitment began for the Manitoba Tomorrow Project

New scientific home
Established at Univ of Toronto

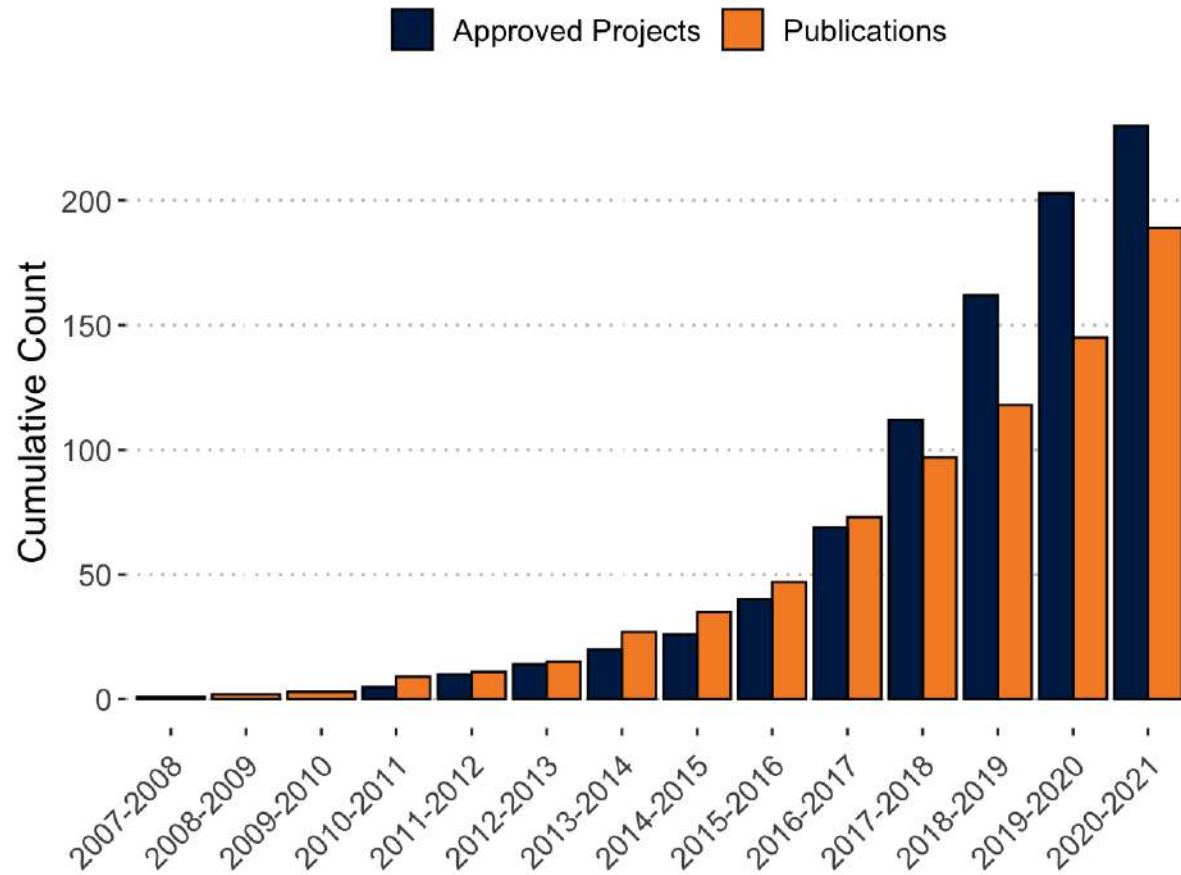
First data made available to the
scientific community

Baseline participant recruitment began

Canadian Partnership for Tomorrow Project (CPTP) launched at the Canadian Partnership
Against Cancer

CanPath

The value of the CanPath platform has increased exponentially since 2008



CanPath is proud to have supported:



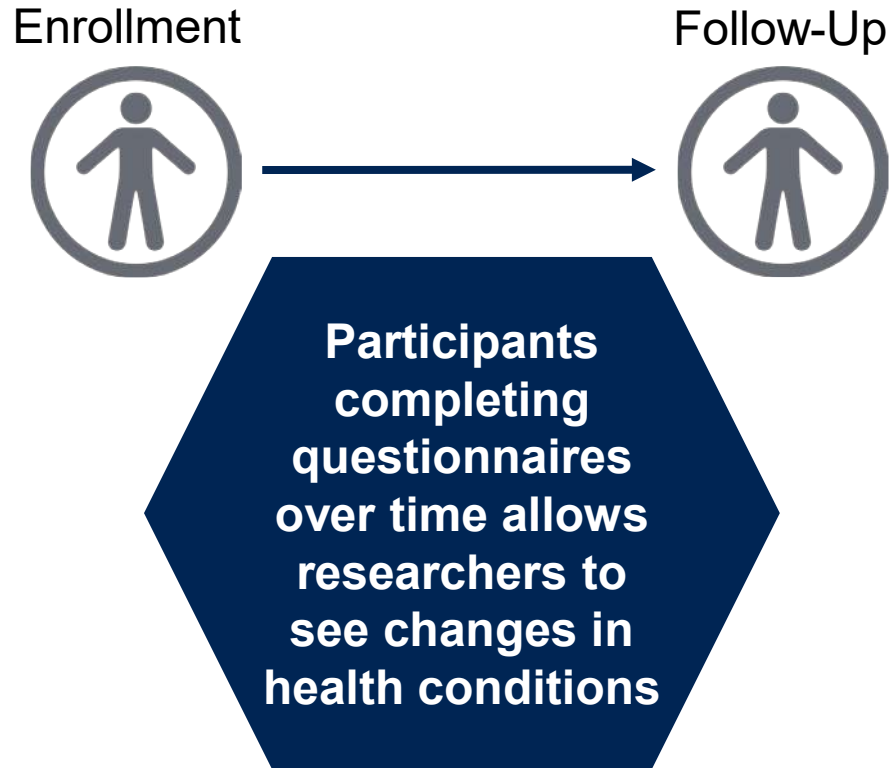
250+ research projects



200+ peer-reviewed publications

Over 330,000 participants have completed detailed questionnaires over the years, with active consent

-  Participant demographics
-  Changes in health status
-  Mental Health
-  Medical history
-  Prescribed medication
-  Family health history
-  Anthropometric measurements
-  Working status
-  Household income
-  Behaviours (sleep, alcohol, tobacco, marijuana use, and e-cigarette use)



Health and lifestyle data in CanPath



Blood

General hematology
Basophils
Eosinophils
Lymphocytes
Monocytes
Neutrophils
White cells
Hb
Hematocrit
MCHC
MCV
Packed cell volume
Platelets
Red cells
RBCDW
HbA1C



Serum

Lipid profile
Cholesterol
HDL-cholesterol
Triglycerides
HDL-ratio
LDL-cholesterol
Glycemia
Glucose
Hepatic function
Electrolytes
Kidney function
Creatinine
Nutritional status
Thyroid function
Uric acid
Thyroxine
TSH



Macro Measures

Arterial stiffness
Cardiac function
Blood pressure
Lung function
Grip strength
Weight
Height
BMI
Waist-hip circumference
Bioimpedance
Depression
Anxiety
Diseases / conditions
Imaging and MRI data



Environmental Measures

Diet questionnaire
Smoking status
Geographical location
Sun exposure
Exercise / sedentarity
Residential history
Income
Education level
Rural / urban
Siblings
Medications
Alcohol consumption
Sleep

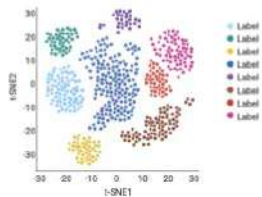
CanPath enables research to investigate the interplay between genetics and the environment through a rich genomics database



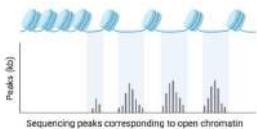
Genotyping (N = 45,000)



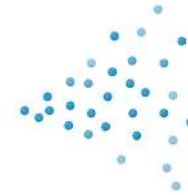
fMRI imaging (N = 10,000)



Single cell RNA sequencing
(N = 400)



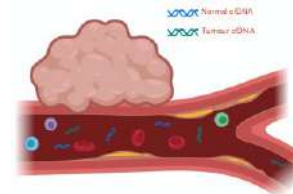
ATAC-seq (Chromatin
Accessibility; N = 400)



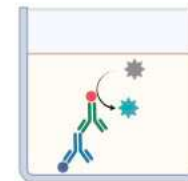
Cytokines/
Inflammatory markers
(N = 20,000)



Bulk transcriptomes
(N = 1,500)



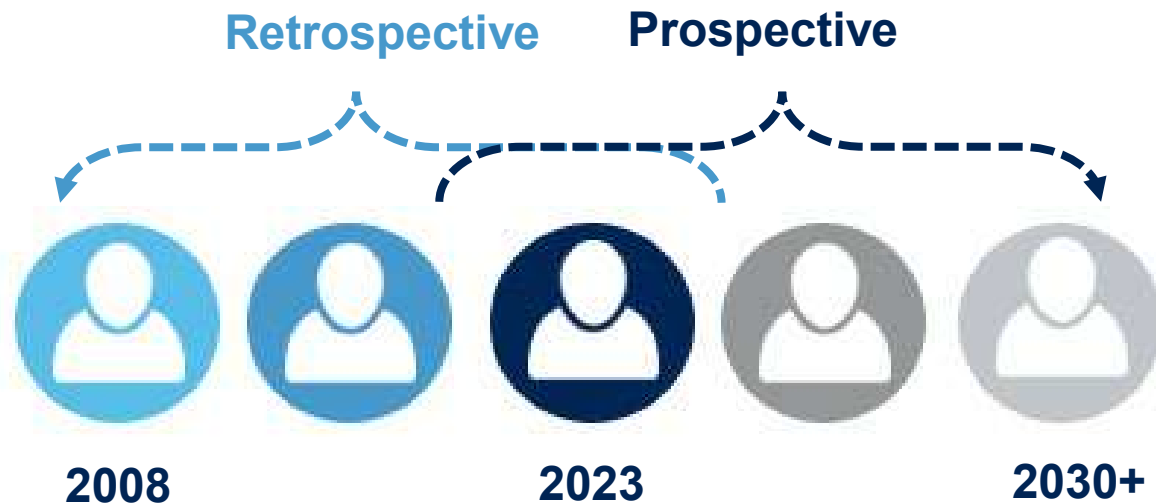
Cell free DNA
methylomes
(N=800)



Serial antibody testing
(high risk for COVID-19,
N = 28,000)

Enabling research breakthroughs to improve the health of Canadians

- CanPath enables research across health domains to improve disease **prevention, detection, treatment and health services**
- CanPath data and biological samples are available to researchers to study **a wide range of exposures (environment, lifestyle, etc.)** and **outcomes (common chronic disease, rare disease, infectious disease, etc.)**
- The longitudinal nature of CanPath enable scientists to perform health-related research **today and for years to come**



CanPath tackles a leading cause of death by supporting cancer research from coast to coast

We enable cutting-edge research to better prevent, diagnose and treat one of the leading causes of death worldwide.

One in four Canadians who develop lung cancer have never smoked.

CanPath data allows researchers to identify actionable lifestyle and behavioral changes to prevent lung cancer in never smokers

Research Lead: Dr. Rachel Murphy (UBC)

Arsenic in drinking water is a public health issue affecting hundreds of millions of people worldwide

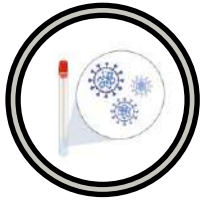
CanPath enables researchers to examine the relationship between cancer and arsenic in drinking water

Research Lead: Dr. Trevor Dummer (Dalhousie & UBC)

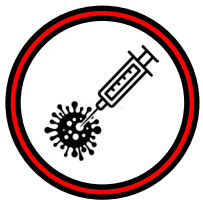
SUPPORT-Canada: A national COVID-19 serological surveillance study



Collection of COVID-19 related data and outcomes from over 100,000 Canadians (beginning in March 2020)



Longitudinal serological surveillance of SARS-CoV-2 antibodies in diagnosed, symptomatic, asymptomatic and susceptible Canadians



Supporting pre- and post-vaccine immune profiling



\$2.6 million in awarded funds from CIHR



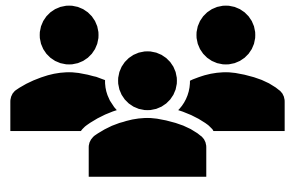
COVID-19 IMMUNITY TASK FORCE

\$5.2 million in awarded funds from PHAC and CITF

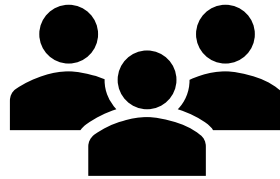


Some participants were invited to provide blood to support antibody profiling

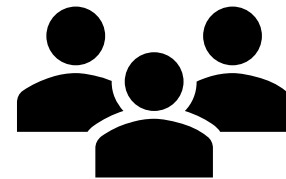
Approximately 28,000 participants were asked to provide a blood sample



Residents of long-term
care homes

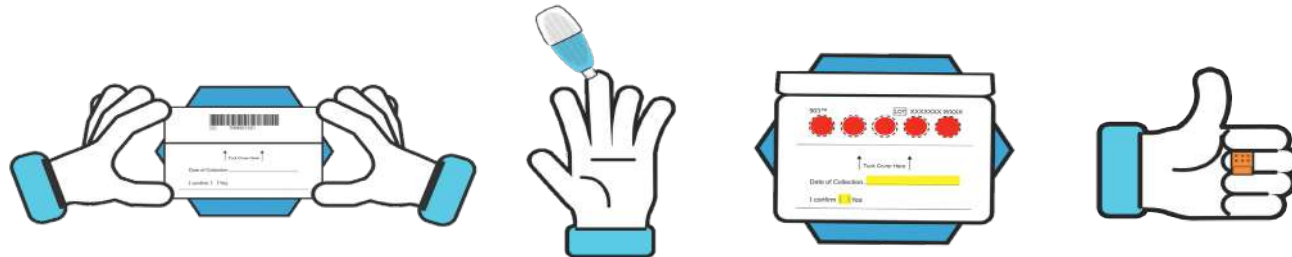


Areas with a high
prevalence of COVID-19

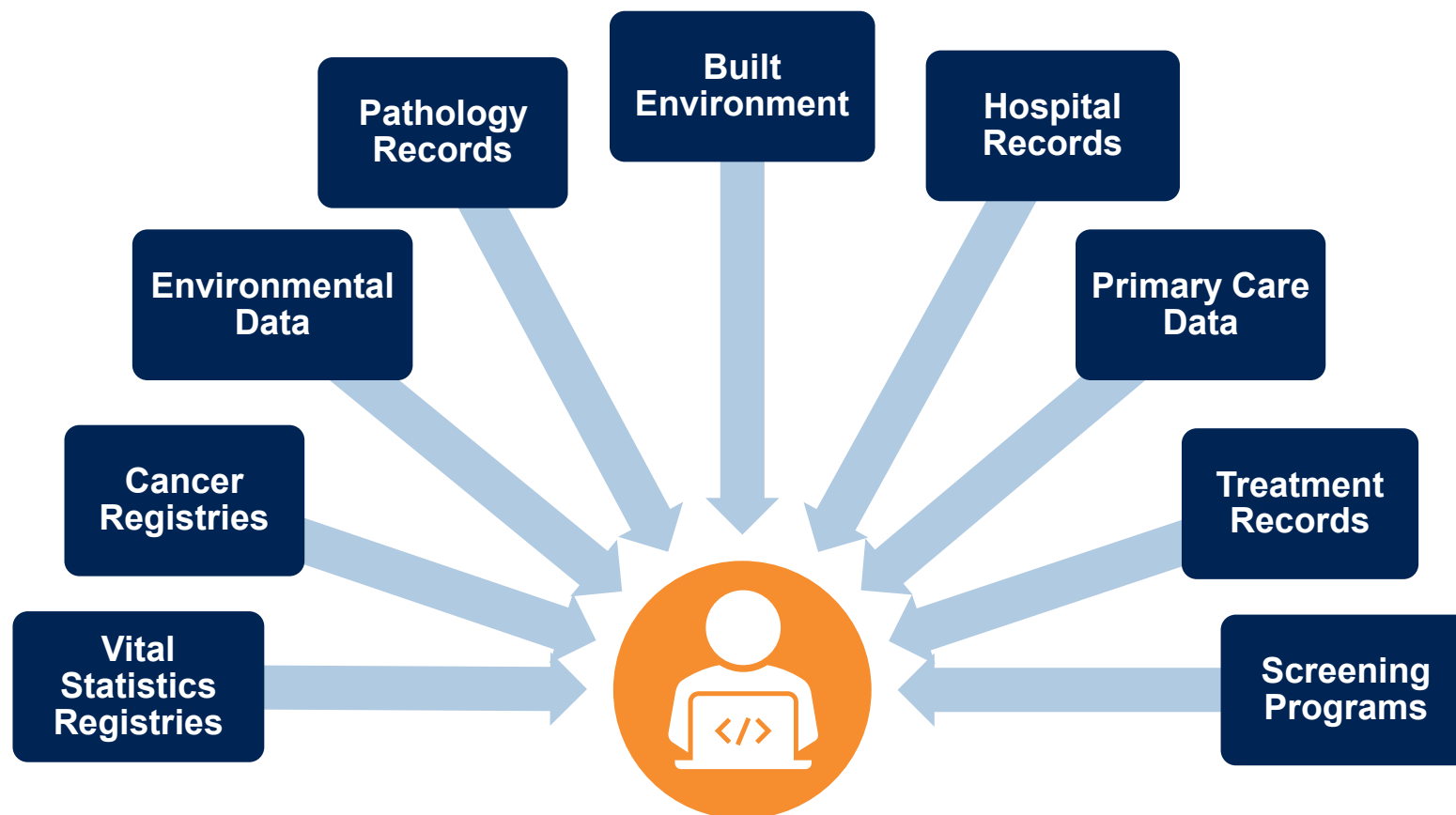


People living in under-
served urban and rural
communities

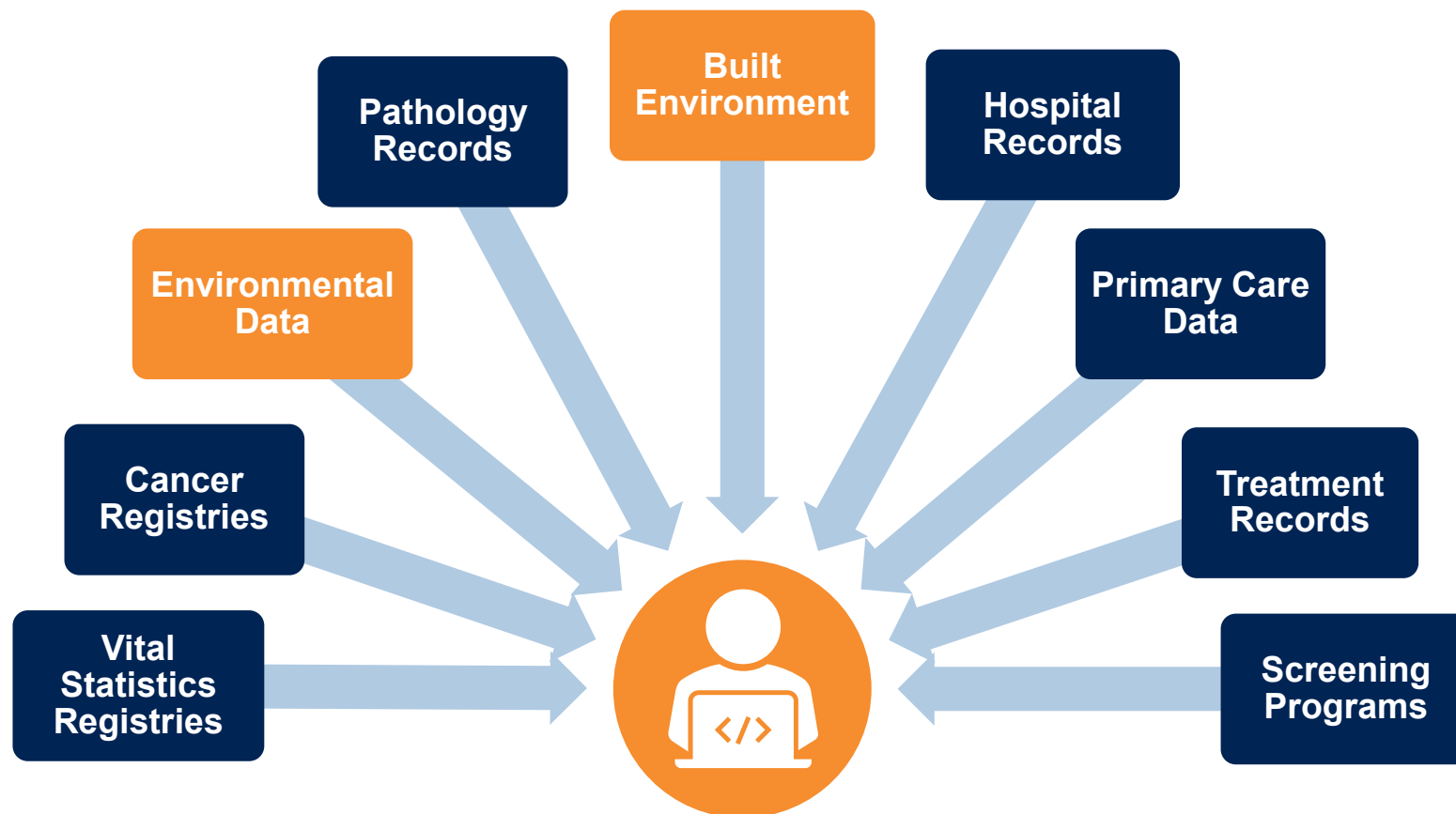
Dried blood spots were mailed to participants to collect blood samples



Data linkages are a CanPath priority as they enable us to evaluate our cohort in real-time



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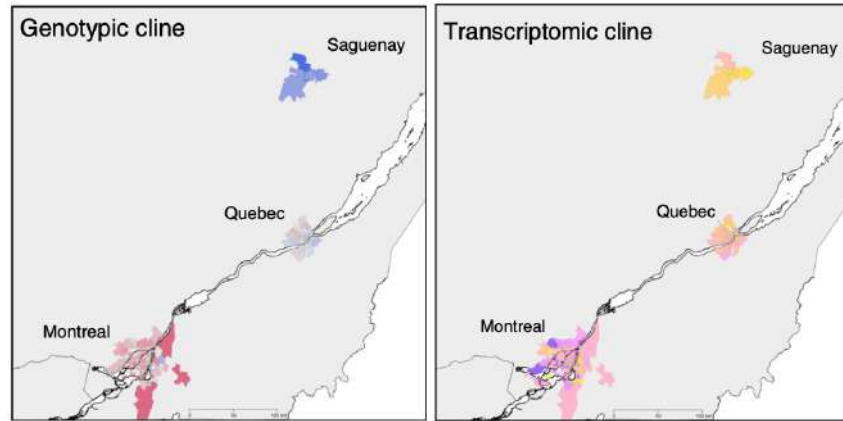


The Canadian Urban Environmental Health Research Consortium

- All CanPath participants have been linked to CANUE environmental exposures
- Every location in Canada can be described by a complex set of environmental factors
- CANUE is building the capacity to study how these multiple **environmental factors are linked to a wide range of health outcomes**



Environment plays a larger role in determining select health outcomes than genetic ancestry



Differential gene expression analysis reveals that the impact of the environment on gene expression and clinical endophenotypes is able to overpower that of genetic ancestry

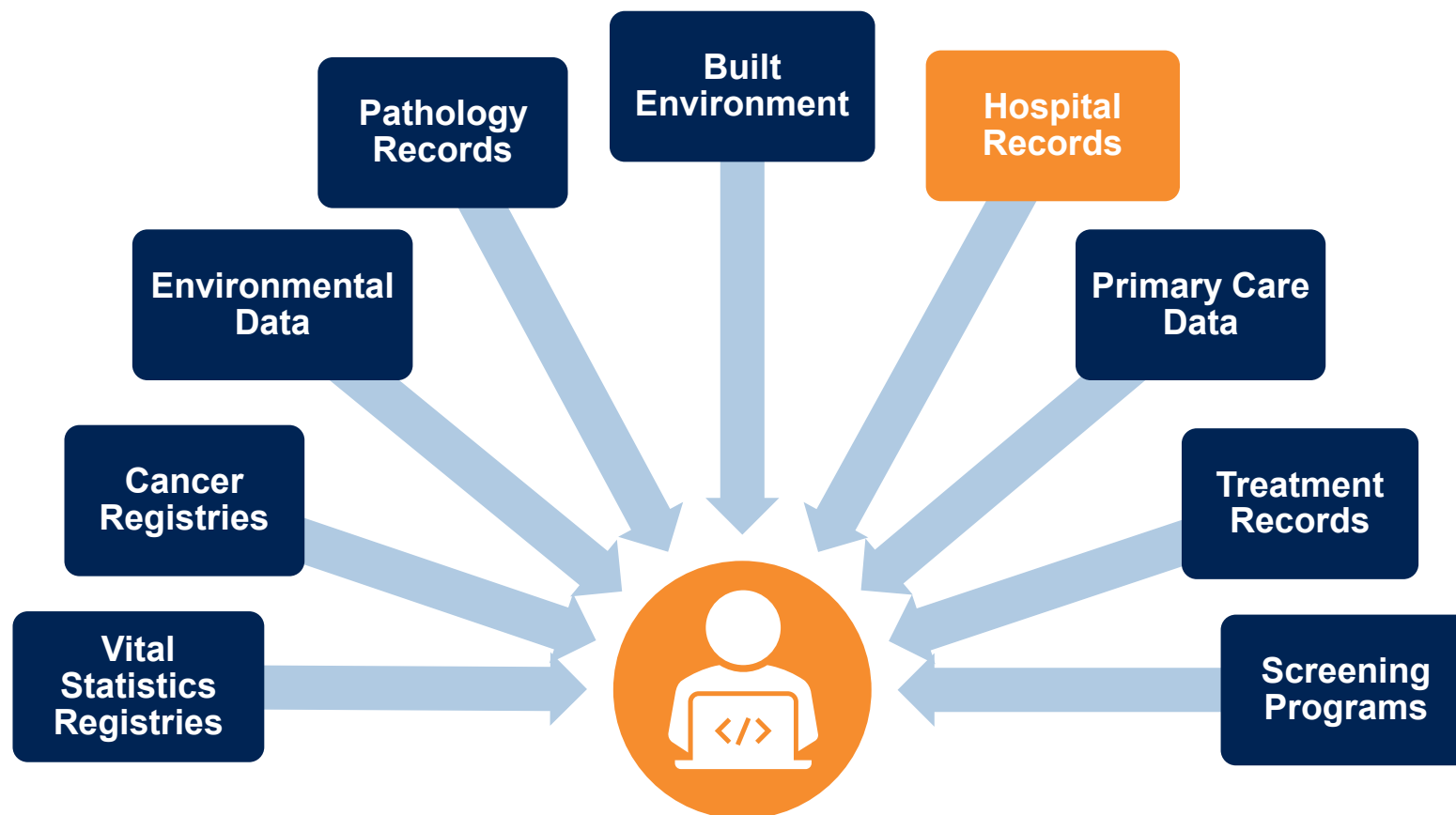


Genetic study of Quebec residents finds air pollution trumps ancestry



"That's really what precision health is about," Dr. Awadalla said. "You want to capture these things before people are in the doctor's office and having to be treated."

Data linkages are a CanPath priority as they enable us to evaluate our cohort in real-time



CanPath will be the first Canadian cohort to host national cohort data and administrative data at a central location

Linkages between the CanPath cohort and the Canadian Institute for Health Information (CIHI) administrative health data are underway.

Individual-level linked CIHI data (N=290,000) will be hosted alongside the harmonized national CanPath dataset and made available to approved researchers requesting administrative health data along with cohort data and/or samples.

CanPath will be the first Canadian program to be able to combine the wealth of cohort resources with national administrative level data in a central location.



Canadian Institute
for Health Information

Institut canadien
d'information sur la santé

The Canadian Cancer Study within the Canadian Partnership for Tomorrow's Health



An overview of the
Canadian Partnership for
Tomorrow's Health



Mapping cancer cases in
CanPath with linkages



Using CanPath to identify
the earliest events in
cancer evolution

Cancer is the leading cause of death in Canada

Cancer poses an enormous burden on both the **health of Canadians and the healthcare system.**

2 in 5 Canadians are expected to develop cancer in their lifetime

Participants in CanPath provide information about their lifestyle, environments, and family medical history, **to help researchers understand the factors that can increase the risk of cancer**

The longitudinal nature of CanPath enables us to focus on **curing cancer**, but also on how to **prevent cancer entirely or capture it early when treatments are more likely to be effective**



Figure reproduced from the Canadian Cancer Society

The Canadian Challenge: Canada has a wealth of health data but there are major barriers to using it

- **Canada has some of the most comprehensive healthcare datasets in the world, but...**
- **Linking and sharing data across jurisdictions is challenging** and represents a major research and public health limitation.
- **Accessing data is cumbersome, costly, and there are major barriers around where data can reside;** all of which limit the extent to which data can be utilised.



CanPath has collected over 1,600 variables on disease outcomes across multiple timepoints

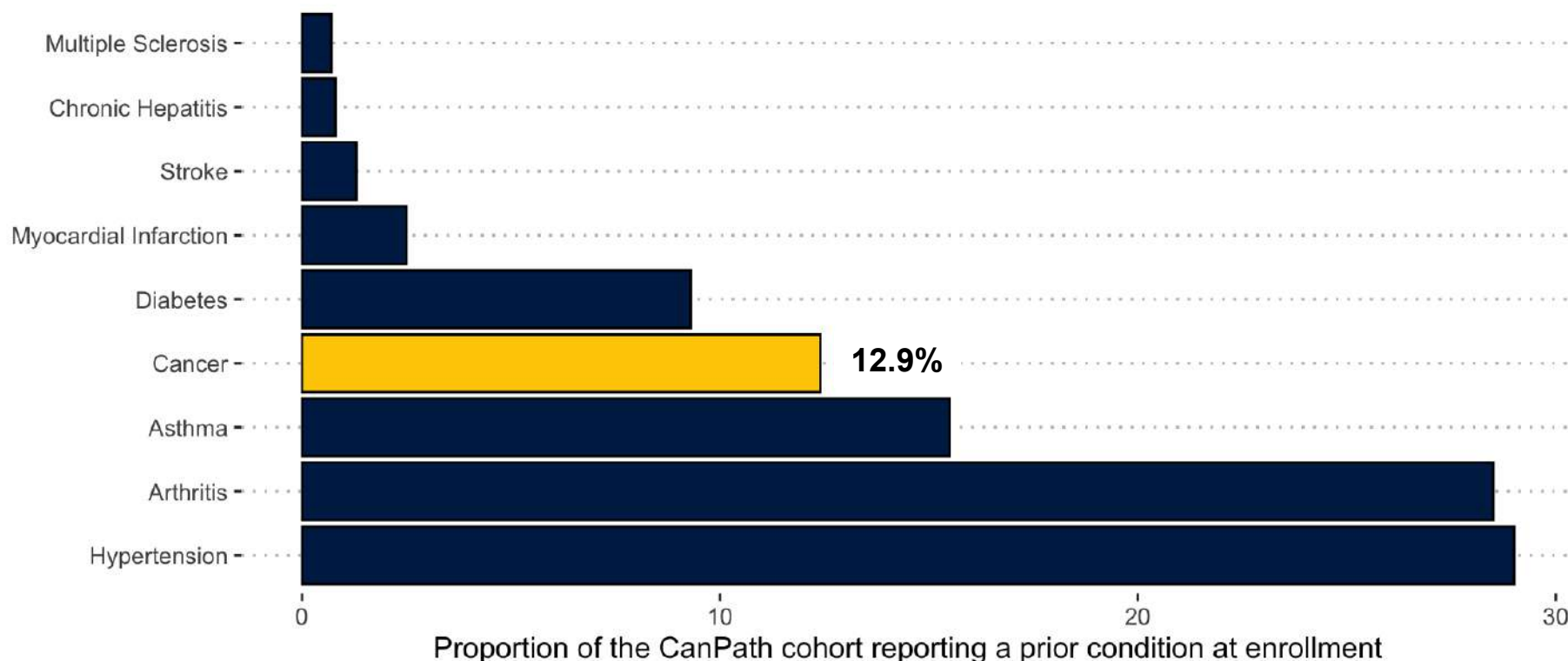
Over
one billion
data
elements
and
growing!

Number of variables collected across disease categories

Pregnancy: childbirth and the puerperium: O00 O9A	0	3	2	0
Neoplasms: C00 D48	200	148	30	29
Mental and behavioural disorders: F00 F99	53	38	22	12
Injury: poisoning and certain other consequences of external causes: S00 T98	2	0	0	0
Endocrine: nutritional and metabolic diseases: E00 E90	49	23	7	4
Diseases without precise specification or falling into multiple categories	0	14	11	5
Diseases of the skin and subcutaneous tissue: L00 L99	18	23	5	5
Diseases of the respiratory system: J00 J99	46	32	11	9
Diseases of the nervous system: G00 G99	58	30	7	4
Diseases of the musculoskeletal system and connective tissue: M00 M99	52	40	13	9
Diseases of the genitourinary system: N00 N99	15	20	5	4
Diseases of the eye and adnexa: H00 H59	53	14	0	0
Diseases of the ear and mastoid process: H60 H95	24	11	2	1
Diseases of the digestive system: K00 K93	136	73	16	12
Diseases of the circulatory system: I00 I99	78	48	19	12
Diseases of the blood and blood forming organs and certain disorders involving the immune mechanism: D50 D89	25	0	2	1
Congenital malformations: deformations and chromosomal abnormalities: Q00 Q99	15	0	0	0
Certain infectious and parasitic diseases: A00 B99	26	14	13	35
	Baseline Qx	Follow-Up Qx	COVID19 Qx 1	COVID19 Qx 2
	Questionnaire			

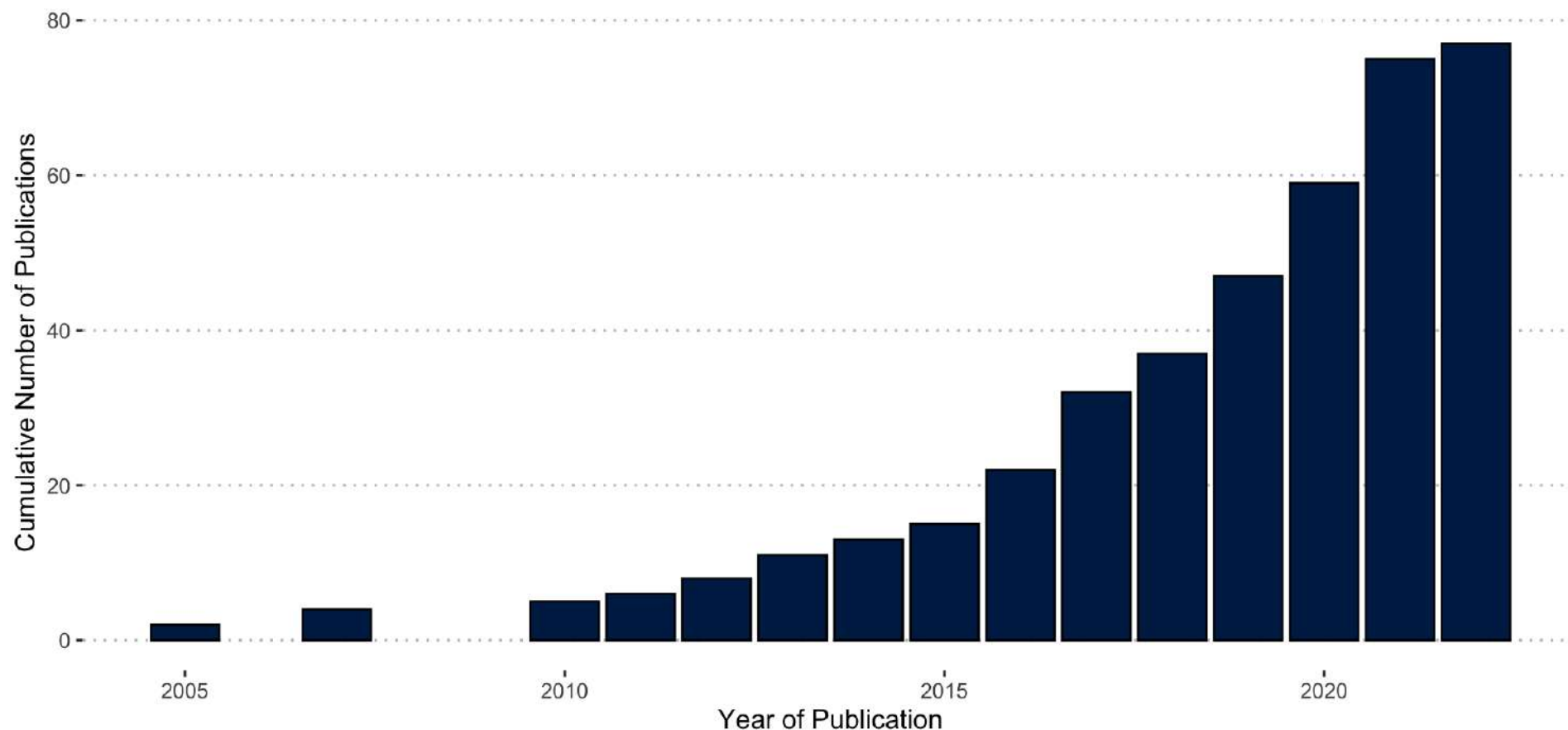
CanPath equips researchers to understand the causes of cancer development and progression

- Over one in ten CanPath participants report a history of cancer at enrollment



The value of CanPath in advancing our understanding of cancer has grown over time

CanPath has supported over 77 publications focused on cancer



Select cancer discoveries supported by CanPath



- Low body mass index, high waist circumference, lower parity, and familial history of breast cancer, were associated with **increased risk of breast cancer diagnosed before age 50**. (Pader J et al., *Cancer Causes Control* 2021)



- Low fruit and vegetable intake and short or long sleep (≤ 6 or > 9 hrs/night) were associated with increased risk of **lung cancer among non-smokers**. (Murphy RA et al., *in submission* 2021)



- A risk score derived from **a small number of genes was found to be predictive of cancer onset** (Duhaze et al. *Frontiers in Genetics* 2021)



- **Insufficient fiber intake was found to increase the risk of cancer development** by 6.3-6.8% for men and 5.0-5.5% for women. (Grundy et al. *CMAJ* 2017)



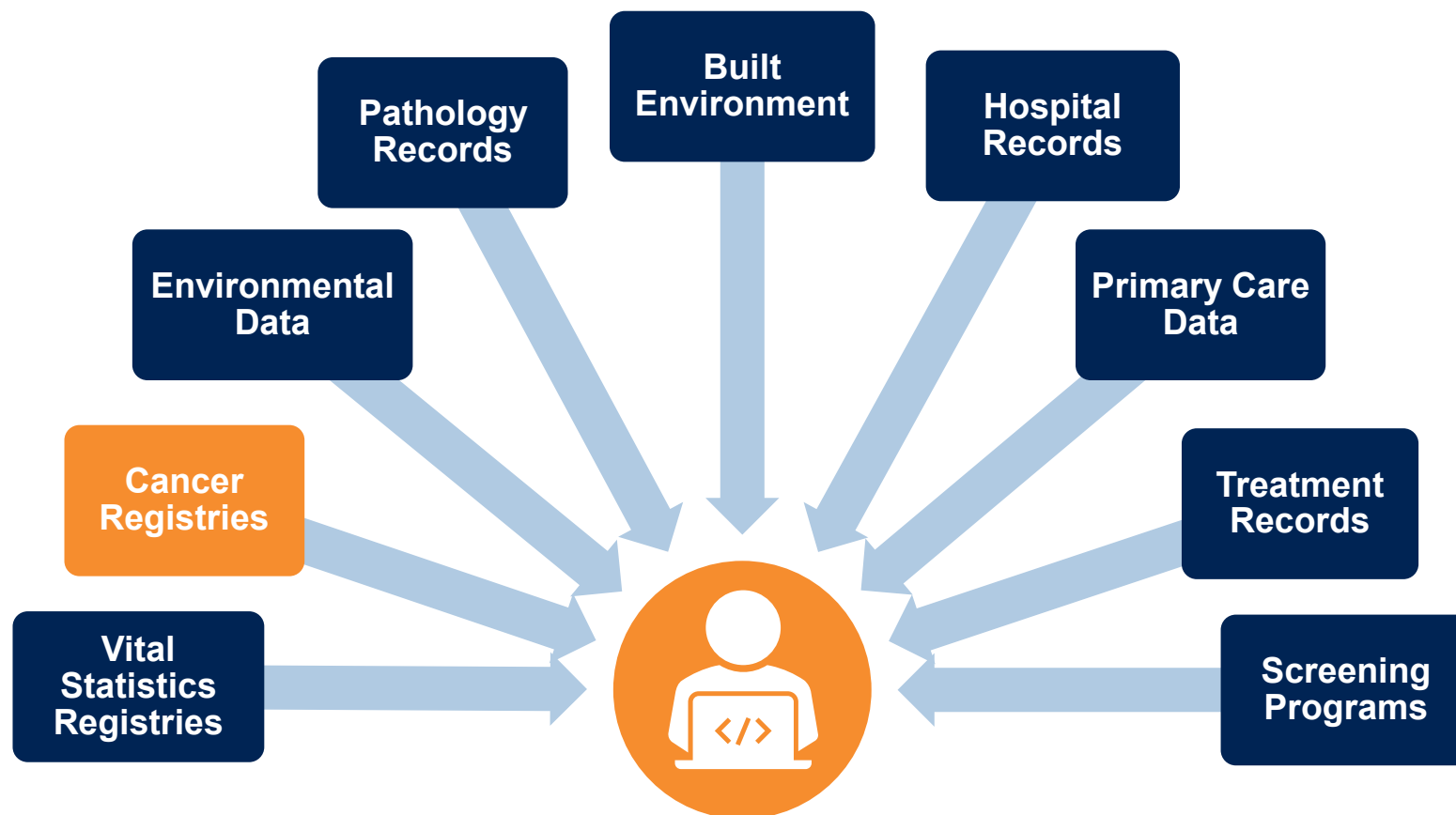
- **Adherence to lifestyle-related cancer prevention recommendations was associated with reduced risk** (13%) of developing cancer. (Whelan HK et al. *Public Health Nutr.* 2019)



- Genetic sequencing of BRCA1- and BRCA2-Negative Families in Canada **identifies novel risk genes for hereditary breast cancer**. (Glentis S et al. *Front Genet.* 2019)

...and many more!

Data linkages are a CanPath priority as they enable us to evaluate our cohort in real-time



CanPath is building the Canadian Cancer Study to advance Canadian cancer research and discovery

- CanPath is building the Canadian Cancer Study to advance research and discovery for the leading cause of death in Canada
- With linked clinical information, we can identify which participants joined the cohort **before developing disease**
- Using samples collected before disease onset, we are able to develop **novel approaches to detect disease years before current methods**
- We are adopting a multi-stage approach to **build the data resources required to enable early cancer prevention and detection research:**
 - Harmonizing aggregate cancer data reporting nationally
 - Hosting linked individual-level cancer outcomes

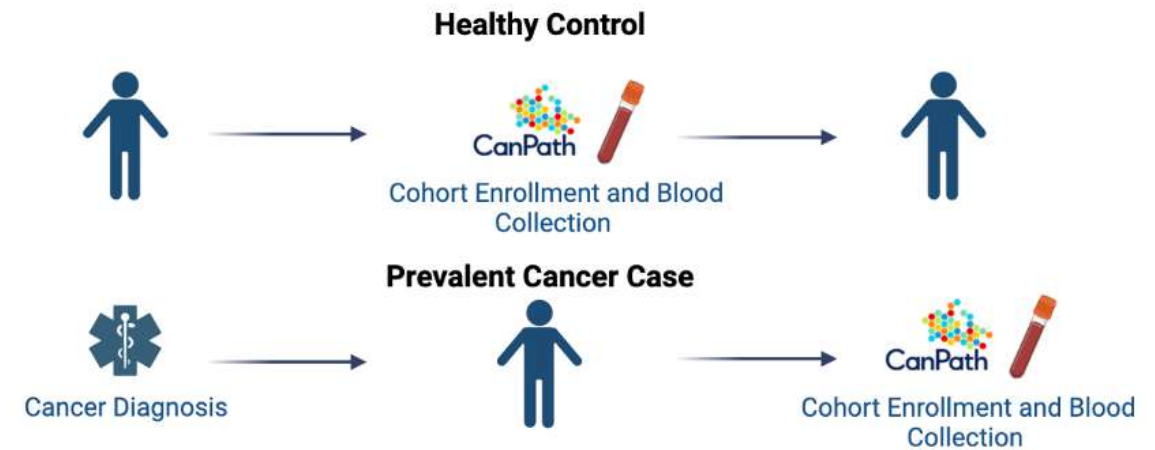
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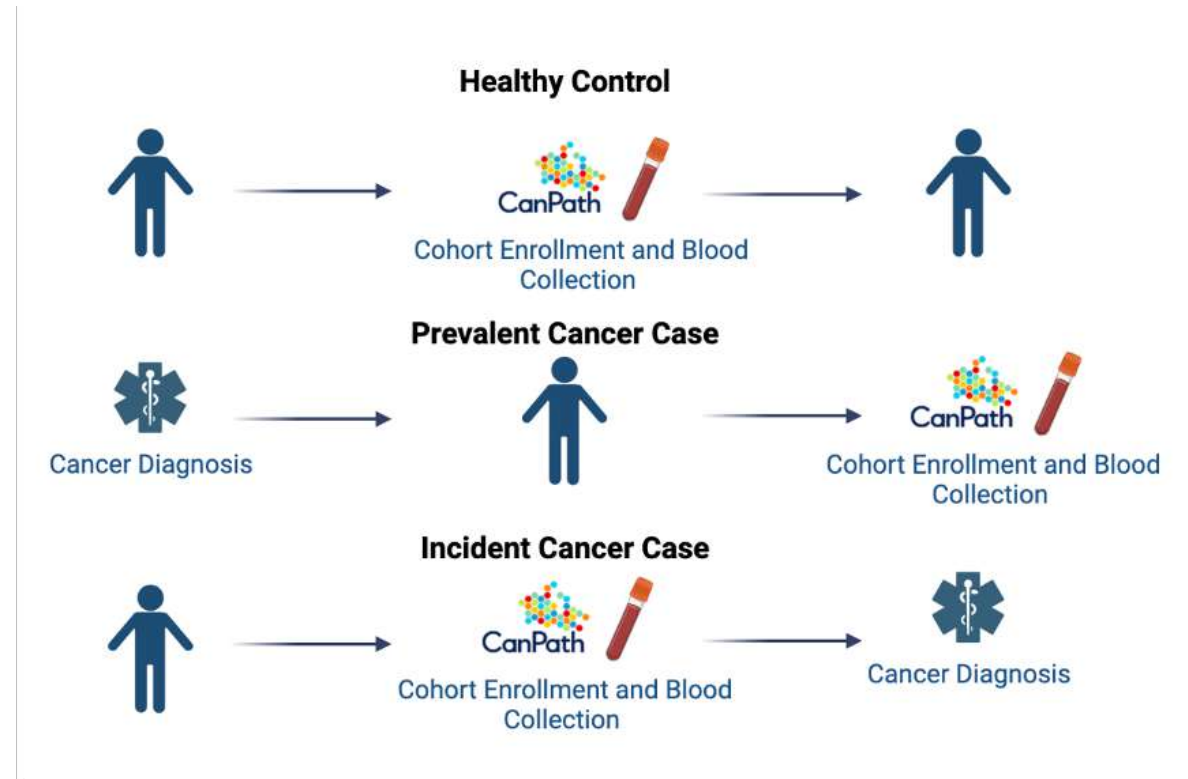
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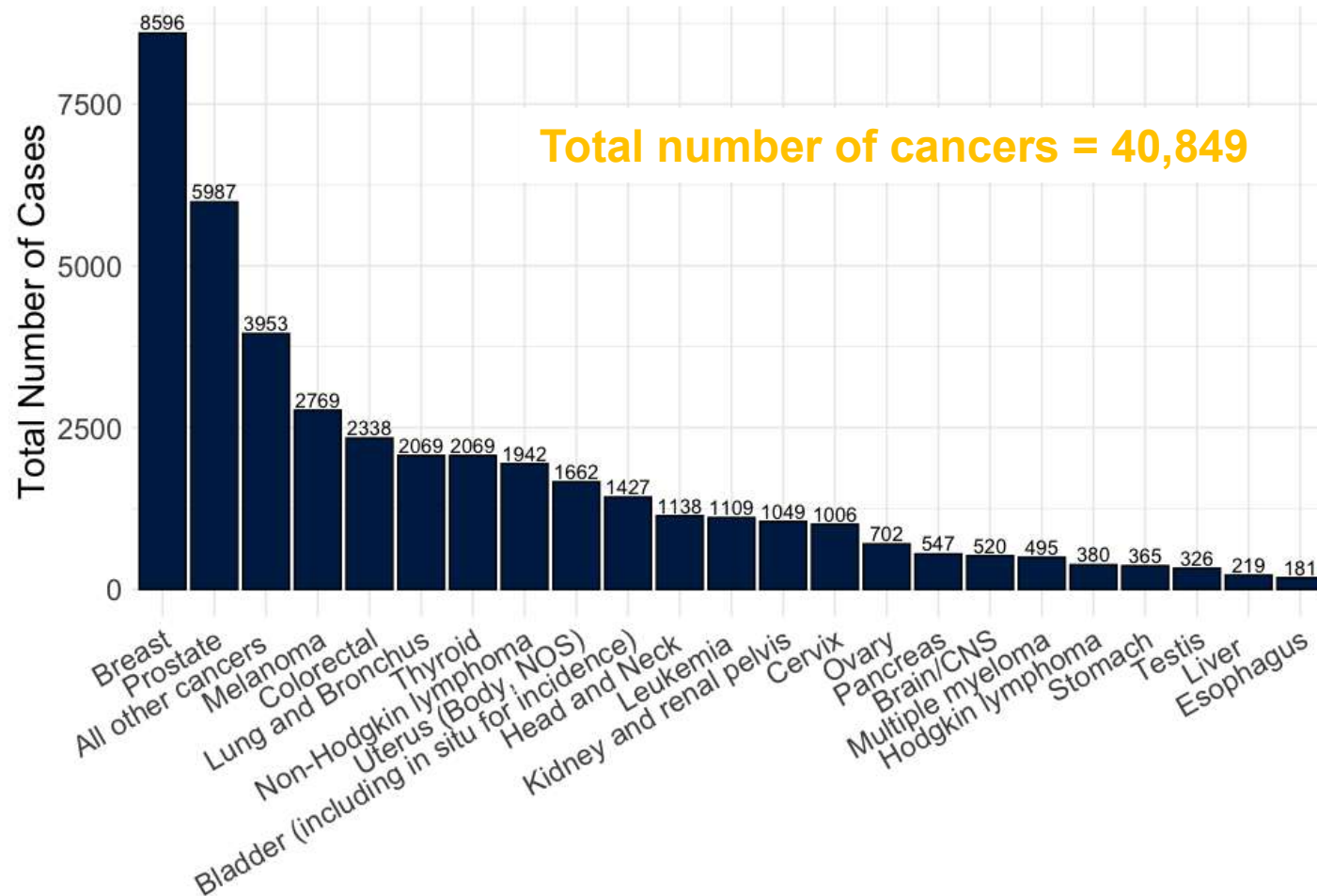


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Mapping cancer cases in the CanPath cohort



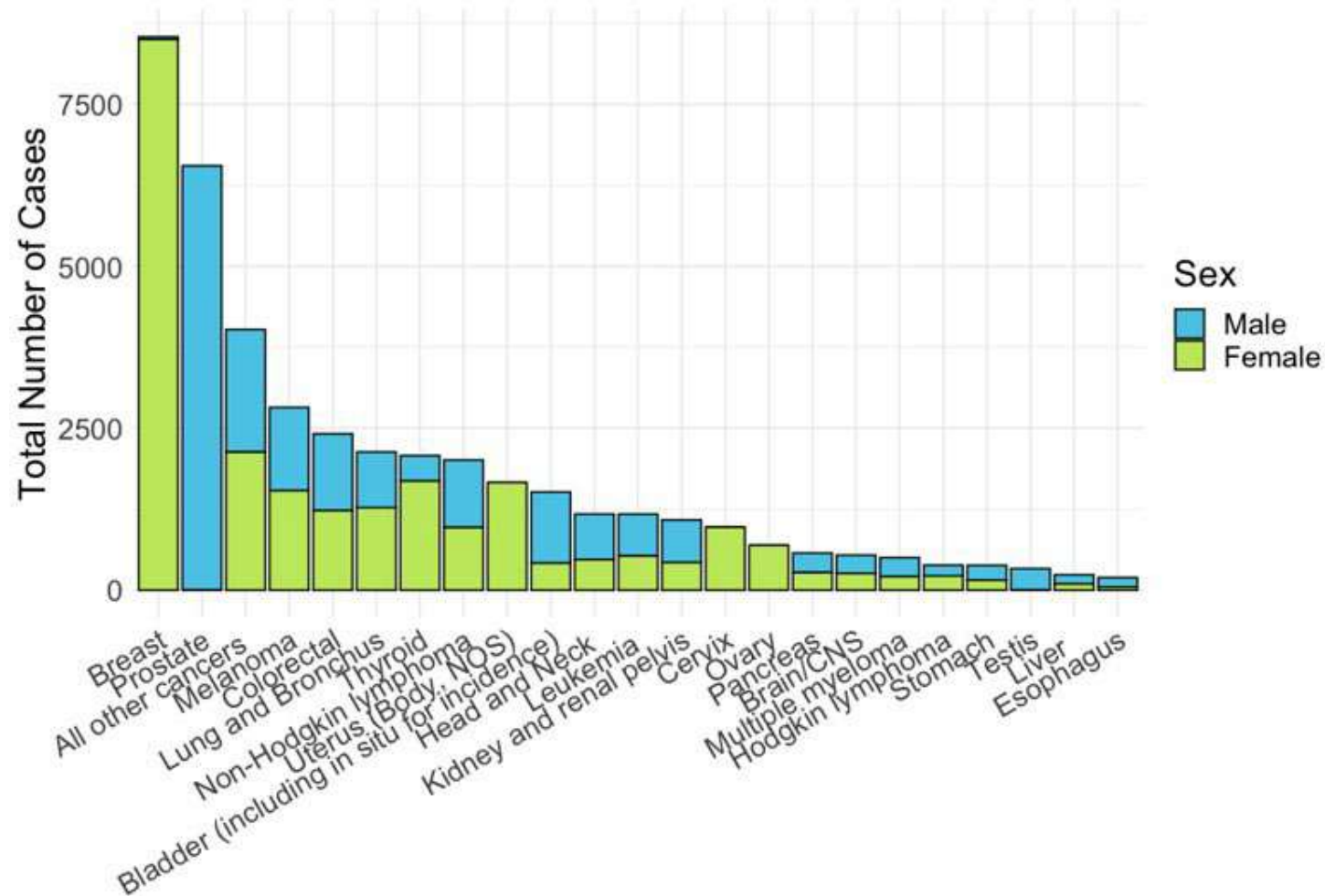
We are leveraging provincial linkages to map map CanPath cancer data and biosample holdings

All cancer data is collected and grouped according to Canadian Cancer Statistic guidelines

Regions included:

- Atlantic Path
- Alberta for Tomorrow Project
- Ontario Health Study
- BC Generations Project

Mapping cancer cases in the CanPath cohort by sex



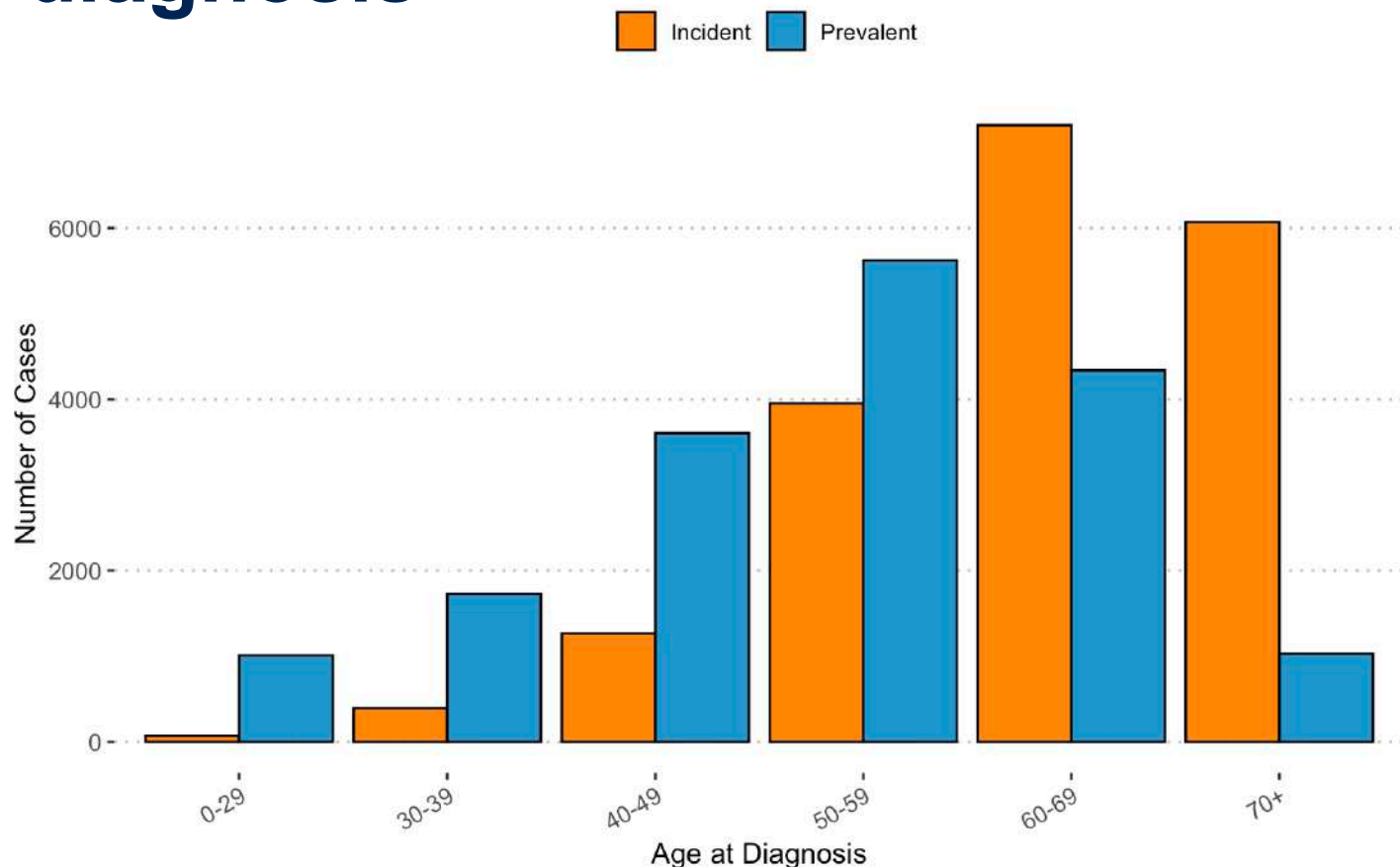
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Mapping cancer cases in the CanPath cohort by age at diagnosis



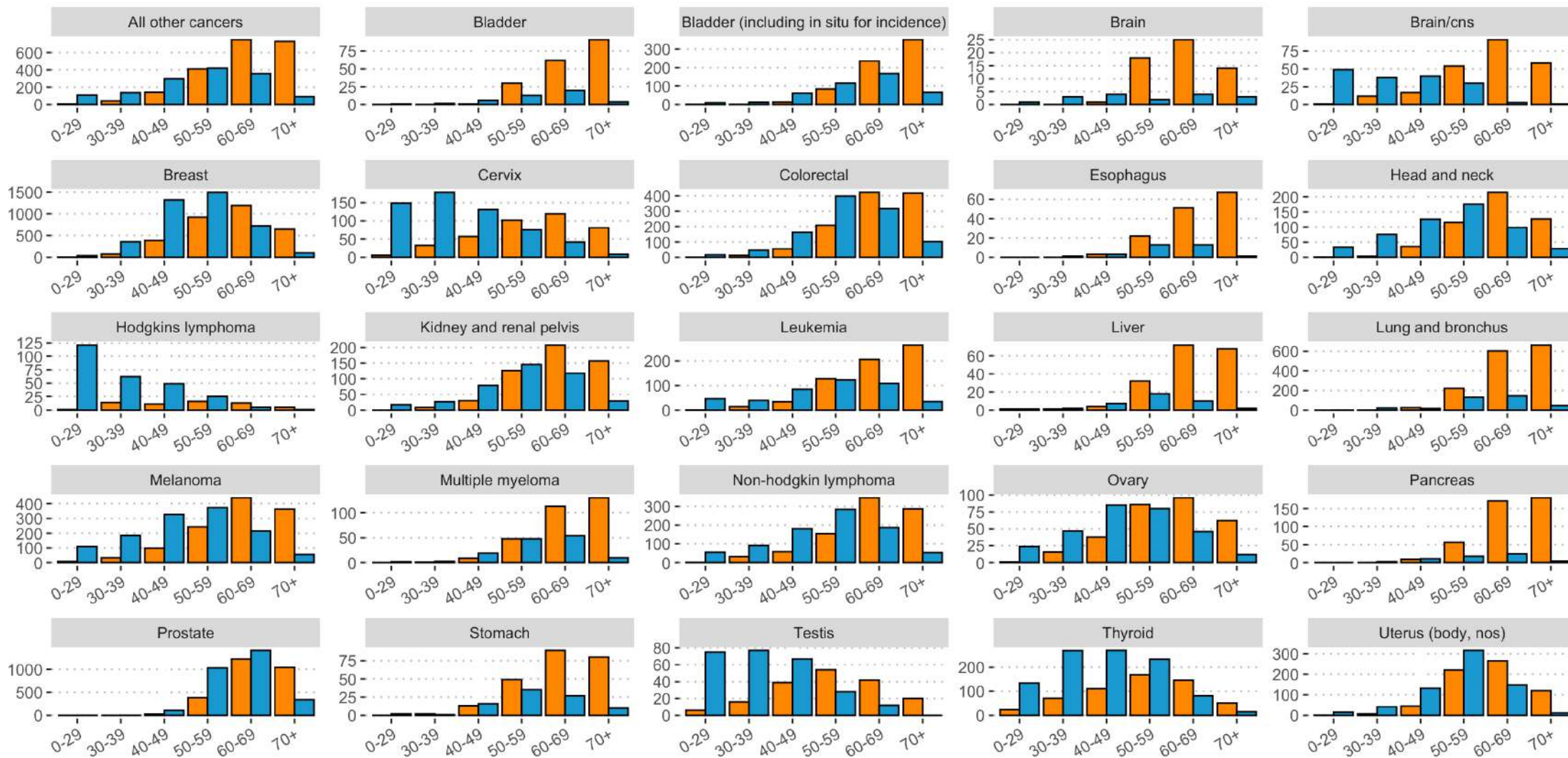
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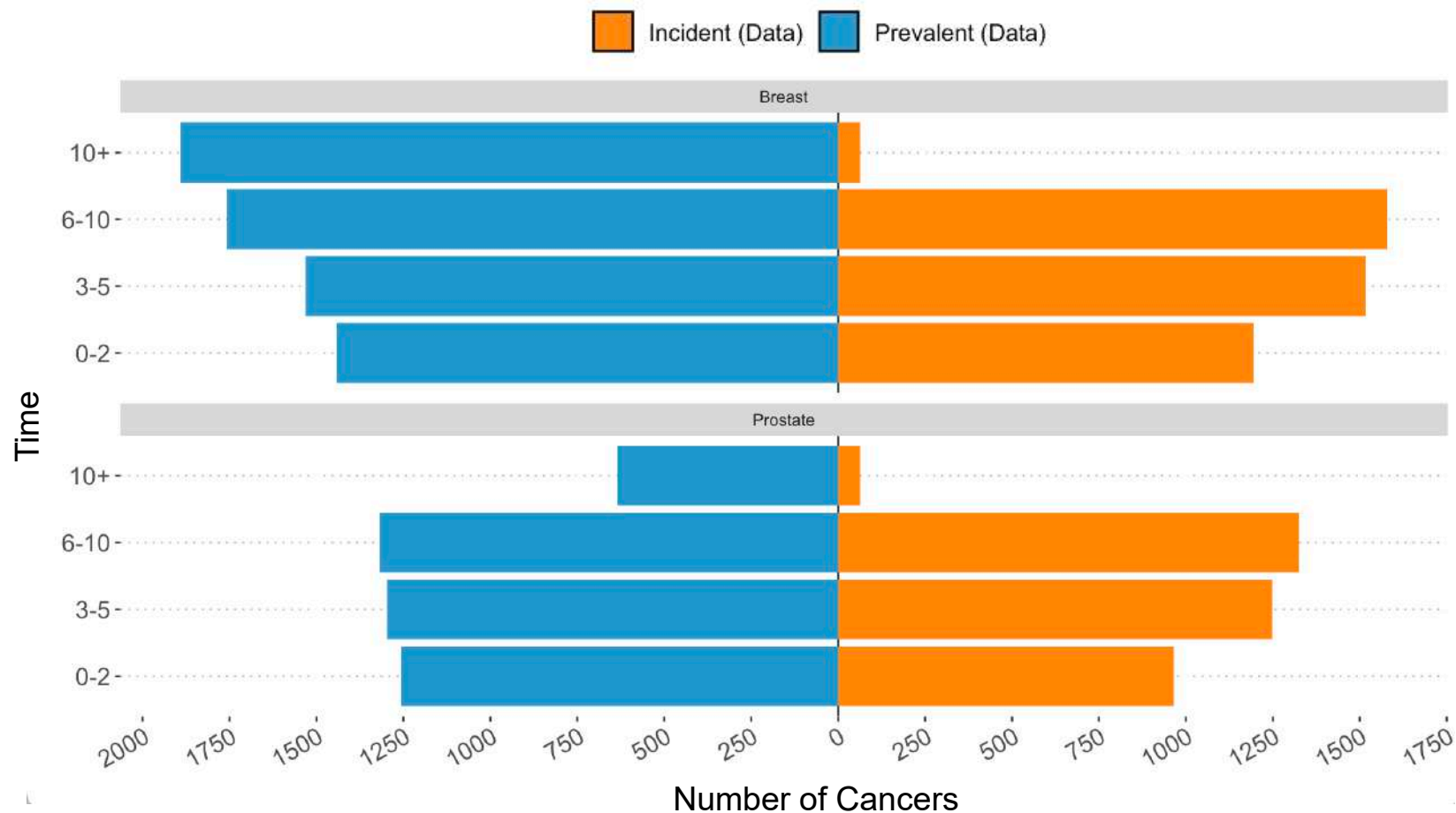
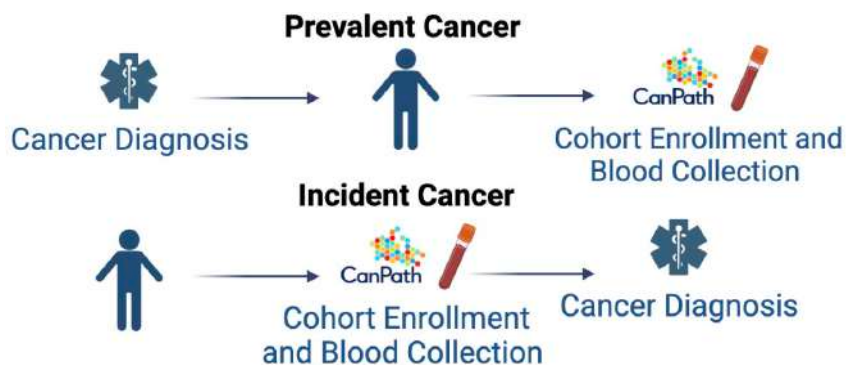
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Incident (Data) Prevalent (Data)

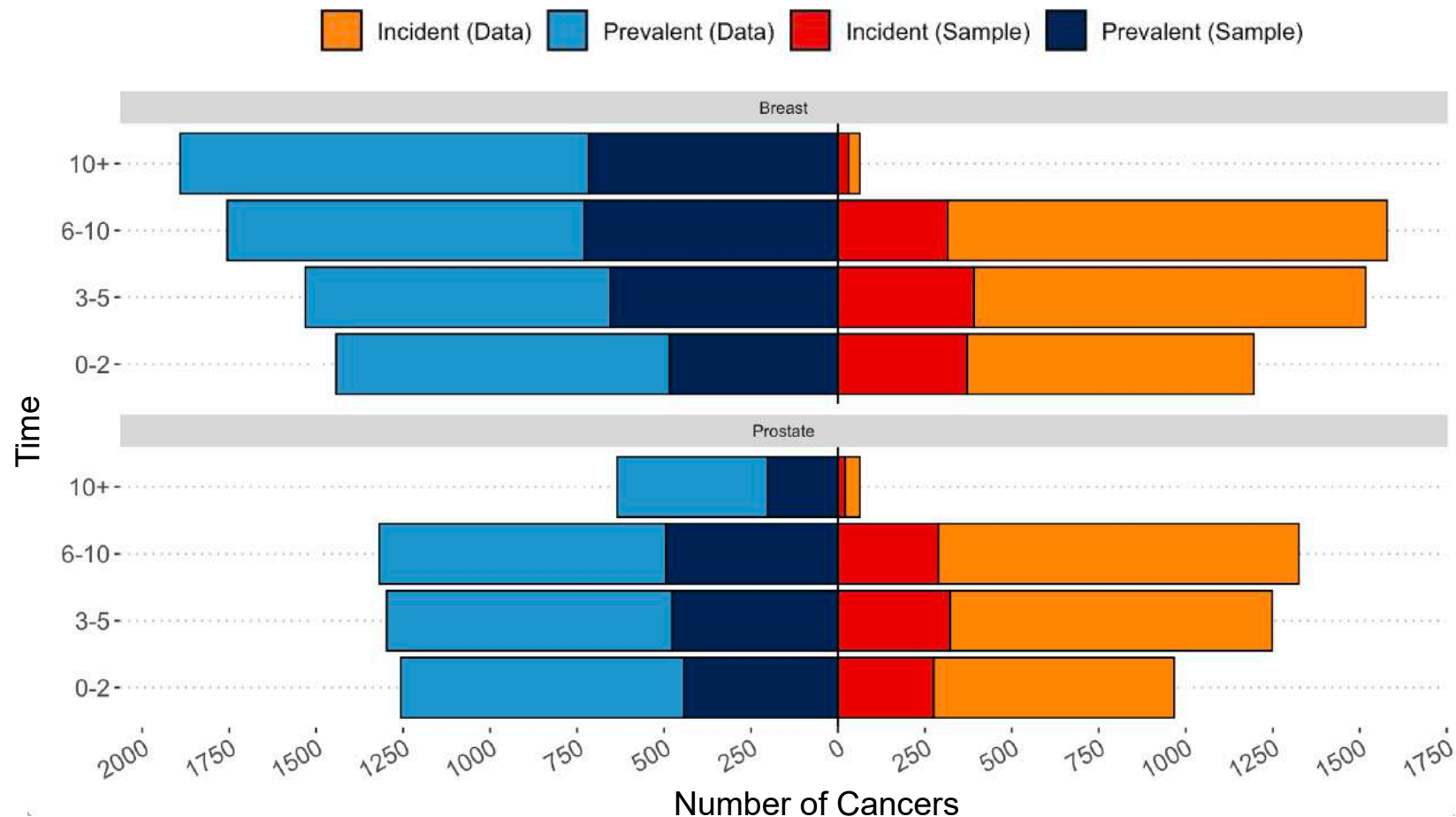
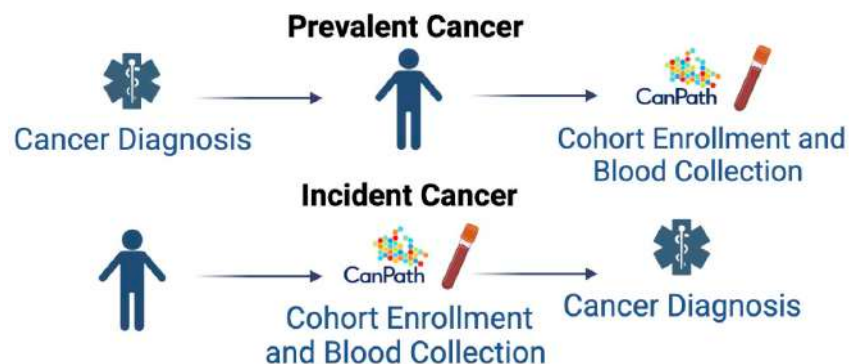


Age at Diagnosis

Linkages enable us to map the time between participant enrollment in CanPath and cancer development

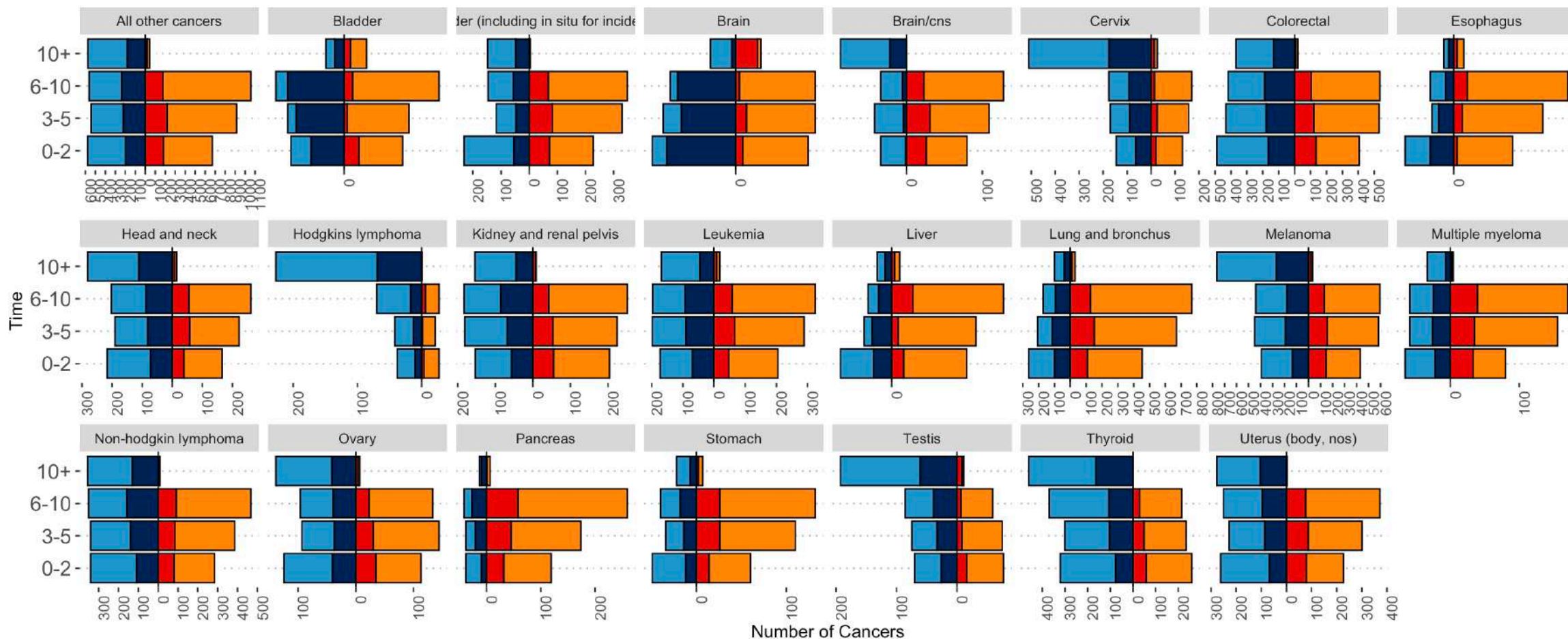


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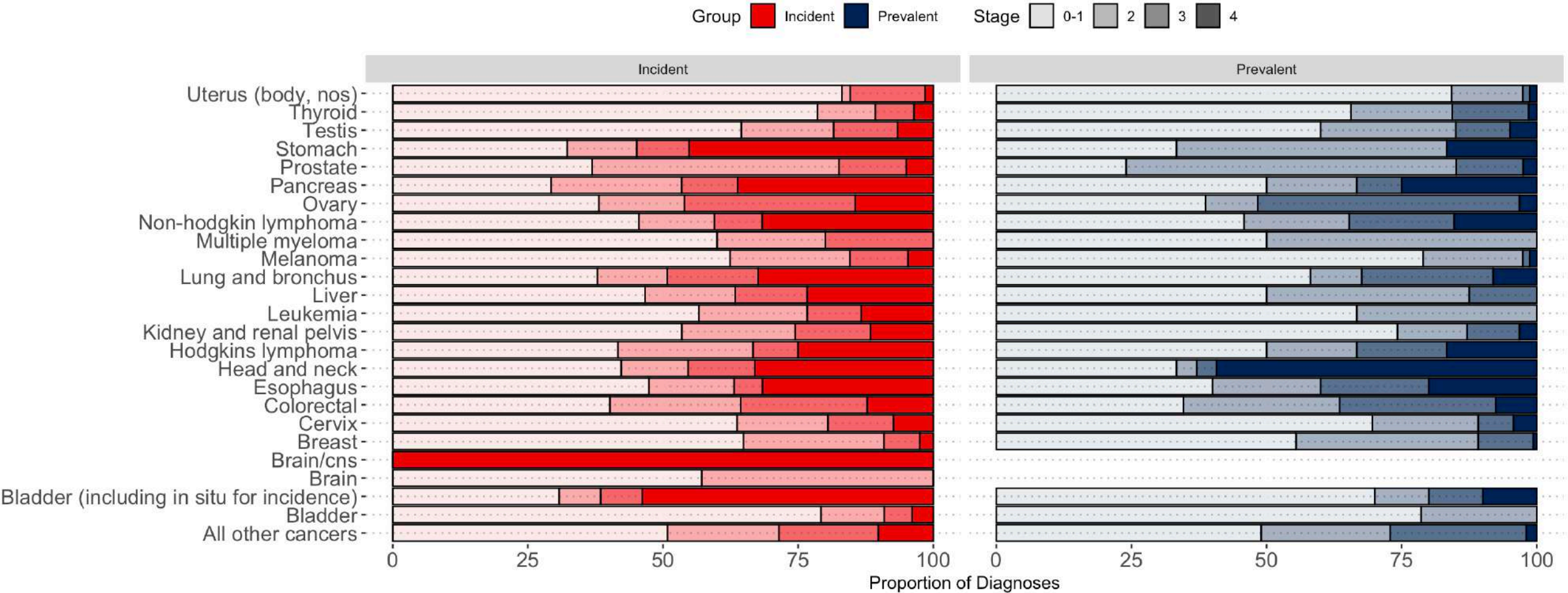


Linkages enable us to map the time between participant enrollment in CanPath and cancer development

Incident (Data) Prevalent (Data) Incident (Sample) Prevalent (Sample)



We can stratify incident and prevalent cases by stage at diagnosis to enable early detection of cancer research



The Canadian Cancer Study within the Canadian Partnership for Tomorrow's Health



An overview of the
Canadian Partnership for
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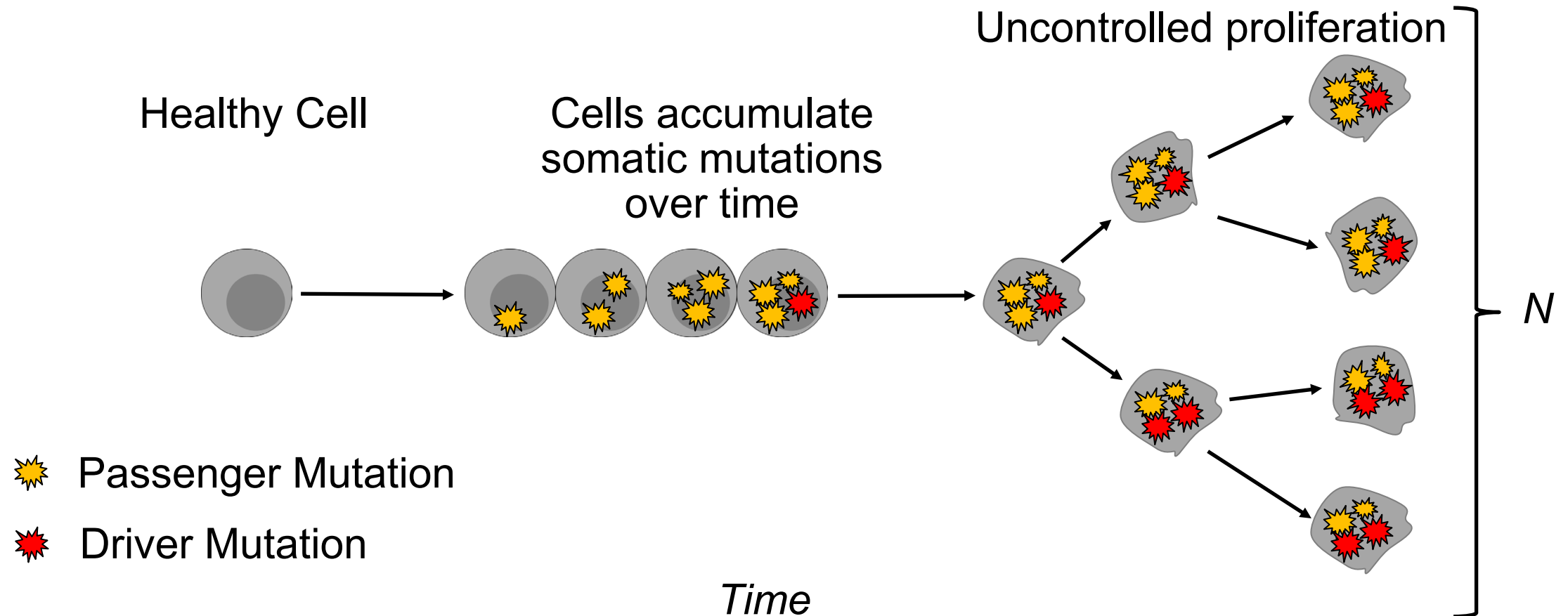


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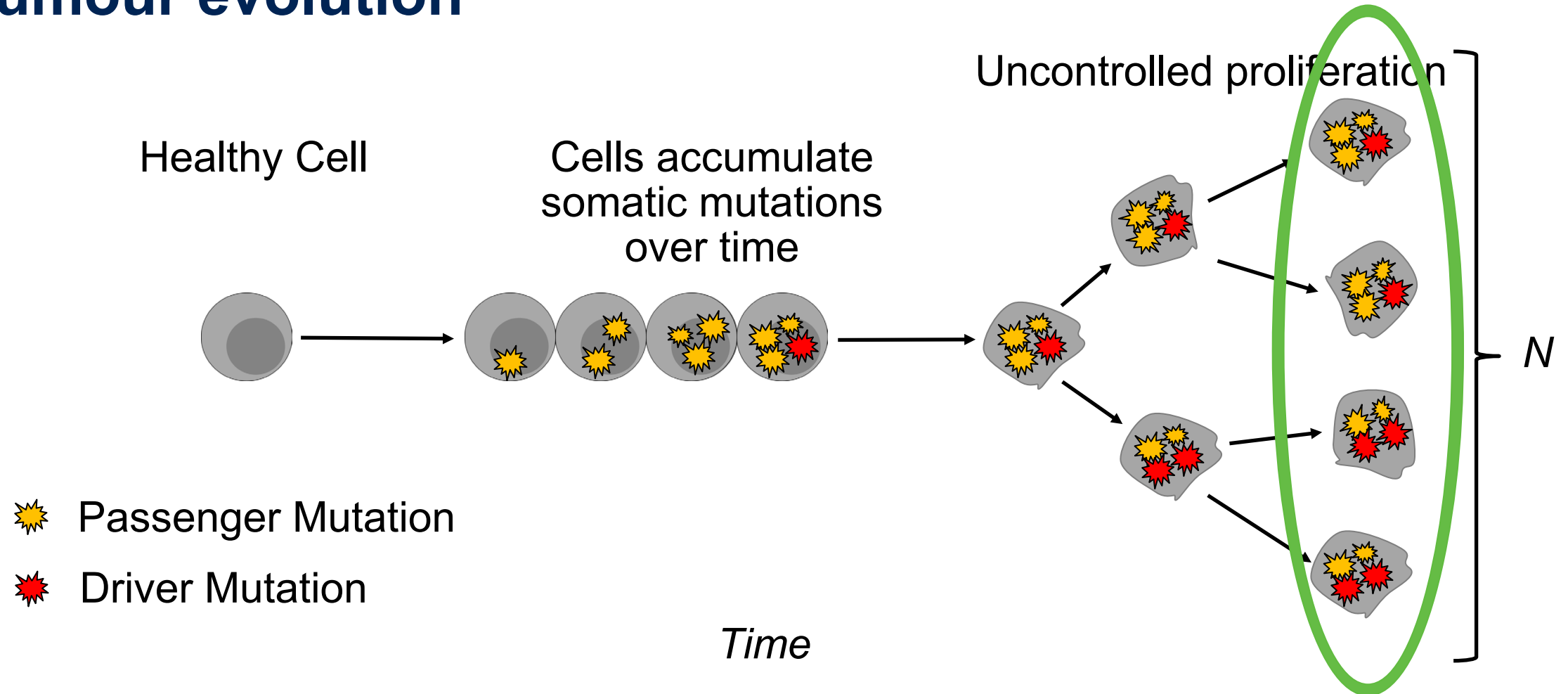


Using CanPath to identify
the earliest events in
cancer evolution

Population genetics tools are frequently used to study tumour evolution

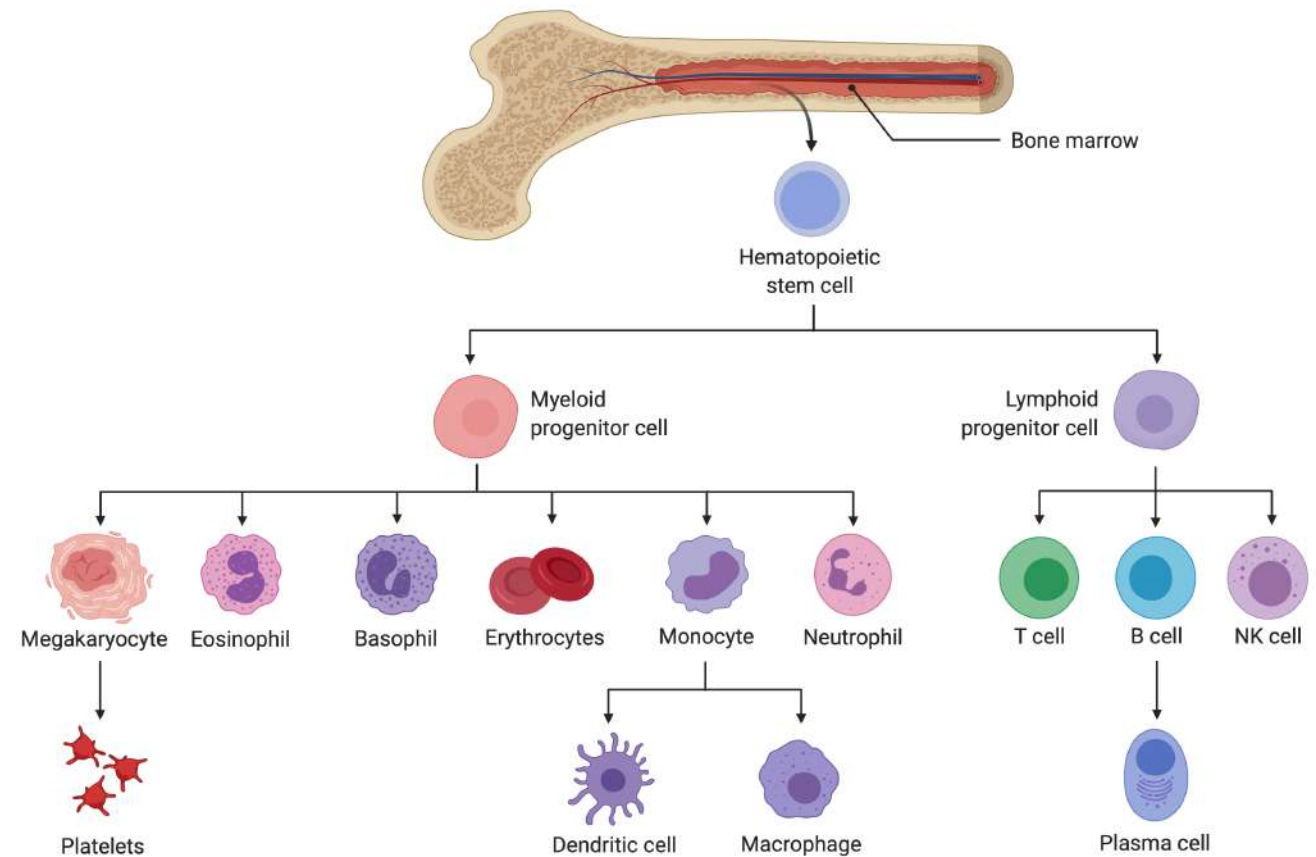


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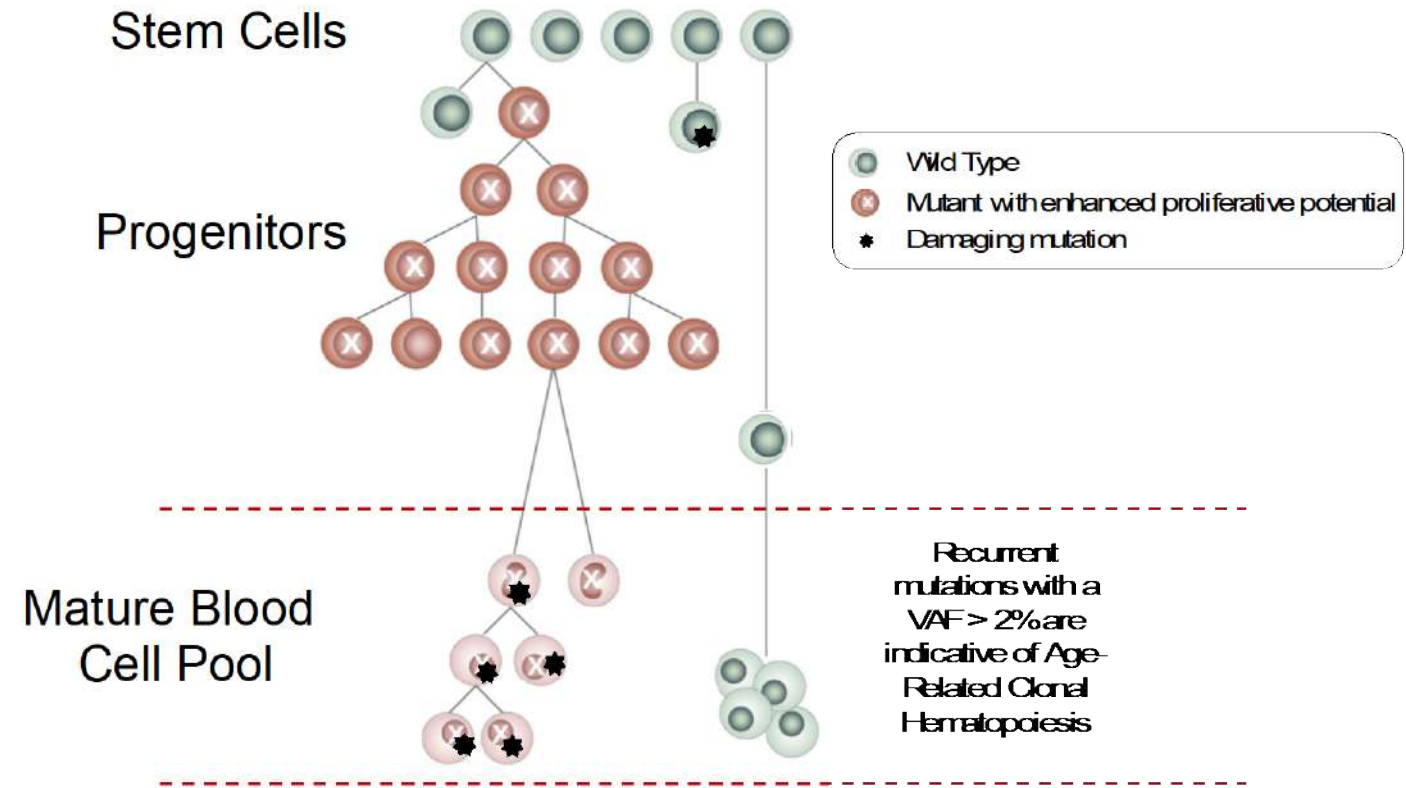
Somatic mutations accumulate in our blood over time

- Blood cell hierarchy derived from **population of stem cells** (HSCs)
- HSC populations are very tightly regulated
- **Age-Related Clonal Hematopoiesis**: the preferential expansion of blood cells that carry recurrent somatic mutations
- ARCH almost inevitable in elderly
- Increased risk of **cancers and cardiovascular disease**



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Jaiswal et al. 2014, Genovese et al. 2014, Xie et al. 2014
Figure adapted from Shlush. Blood (2018)

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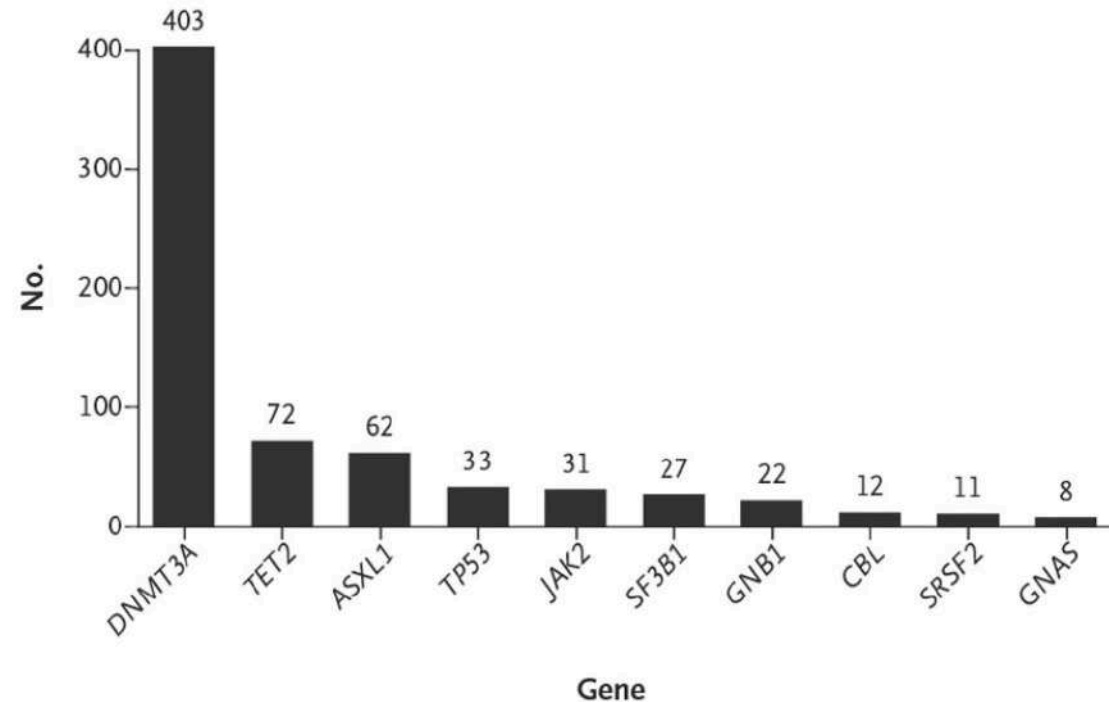


Figure from Jaiswal et al. NEJM (2014)

Somatic mutations accumulate in our blood over time

- Blood cell hierarchy derived from **population of stem cells** (HSCs)
- HSC populations are very tightly regulated
- **Age-Related Clonal Hematopoiesis**: the preferential expansion of blood cells that carry recurrent somatic mutations
- ARCH almost inevitable in elderly
- Increased risk of **cancers and cardiovascular disease**

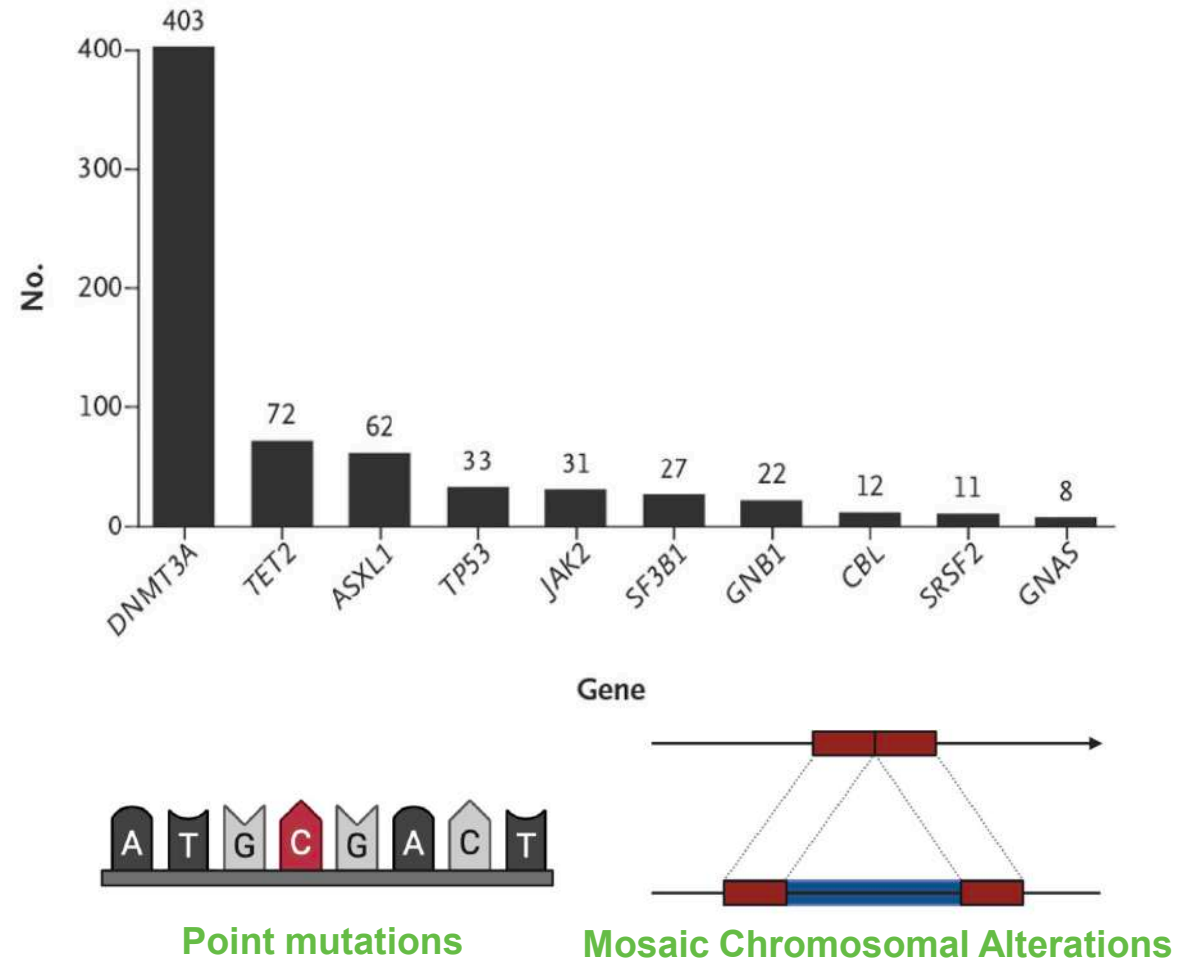
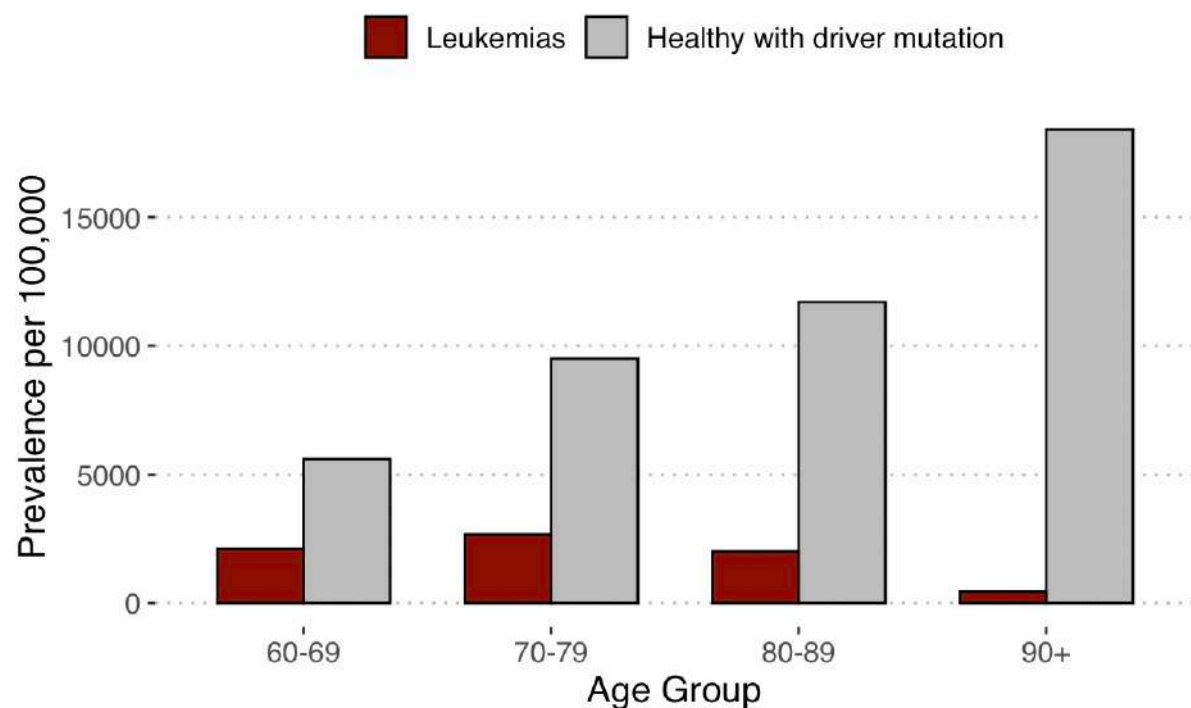


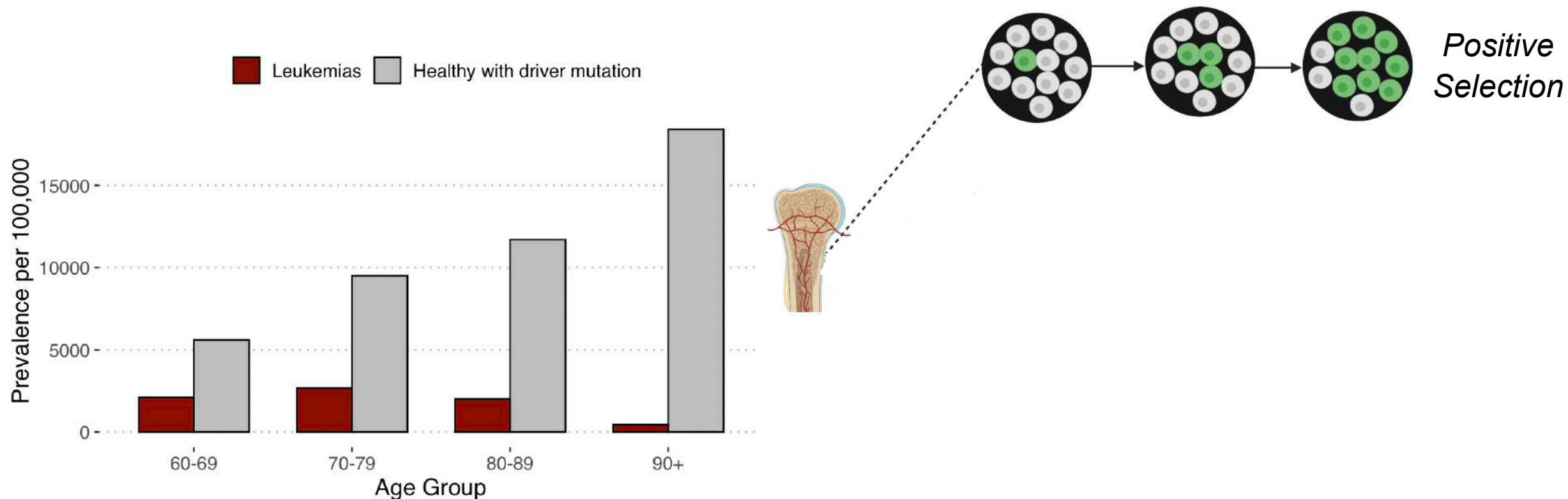
Figure from Jaiswal et al. NEJM (2014), Jaiswal et al. 2014, Genovese et al. 2014, Xie et al. 2014, Loh et al. 2018

Mutations in driver genes are common in healthy individuals



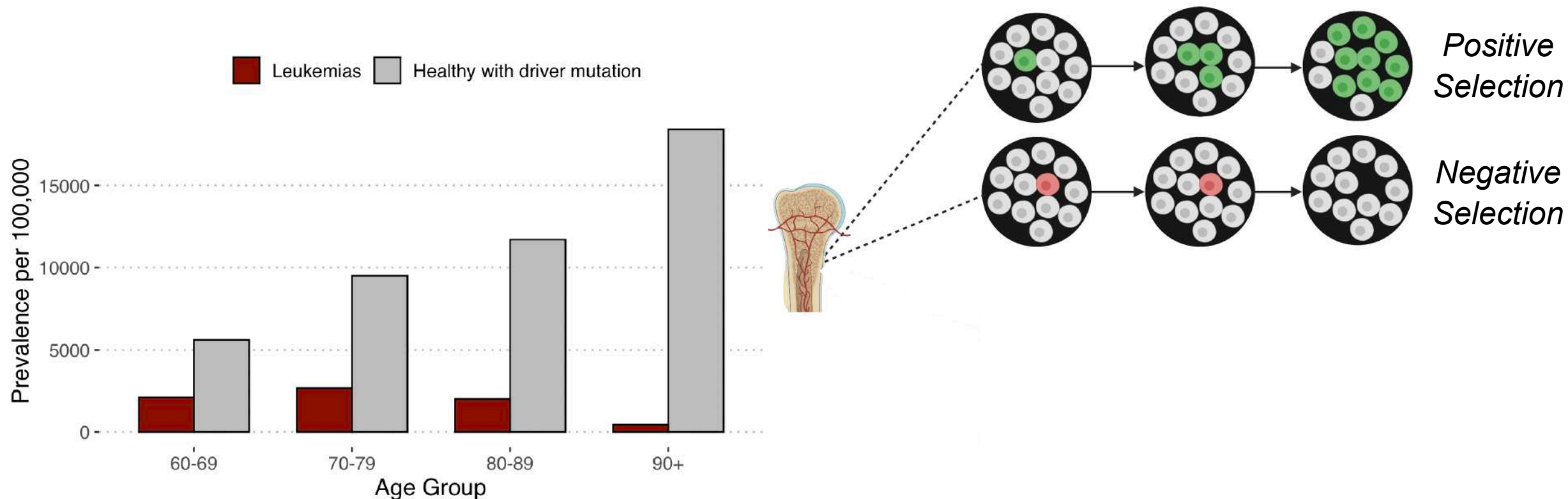
Data from Jaiswal et al. (2014). N Engl J Med

Mutations in driver genes are common in healthy individuals



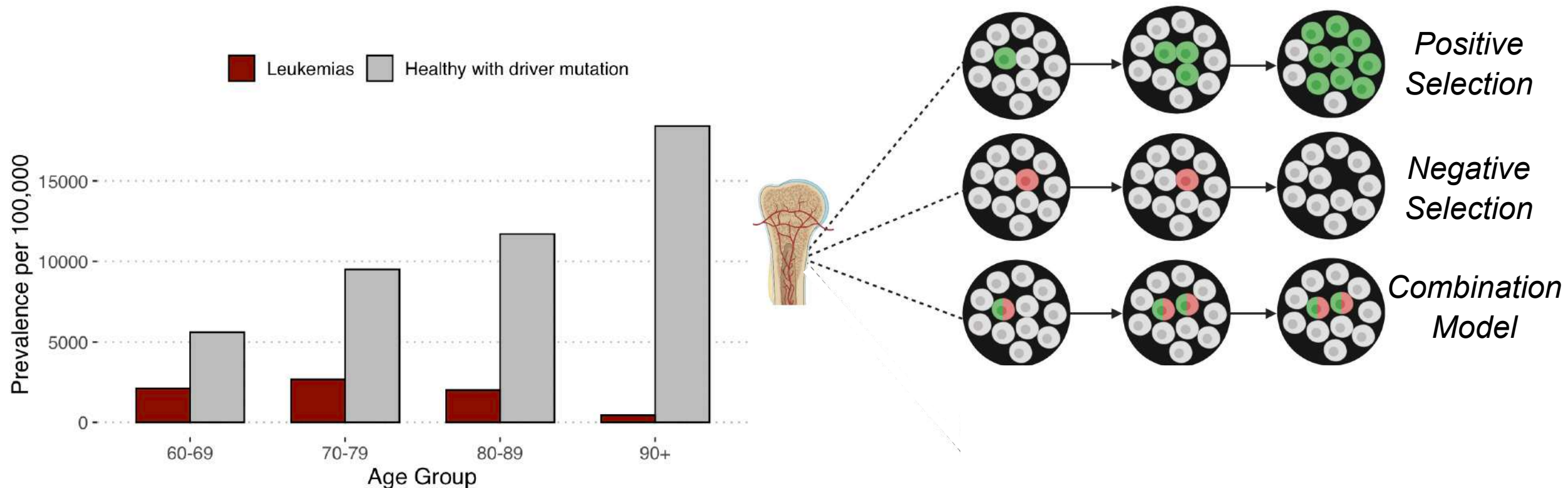
Cairns (1975), Martincorena et al. 2017

Mutations in driver genes are common in healthy individuals



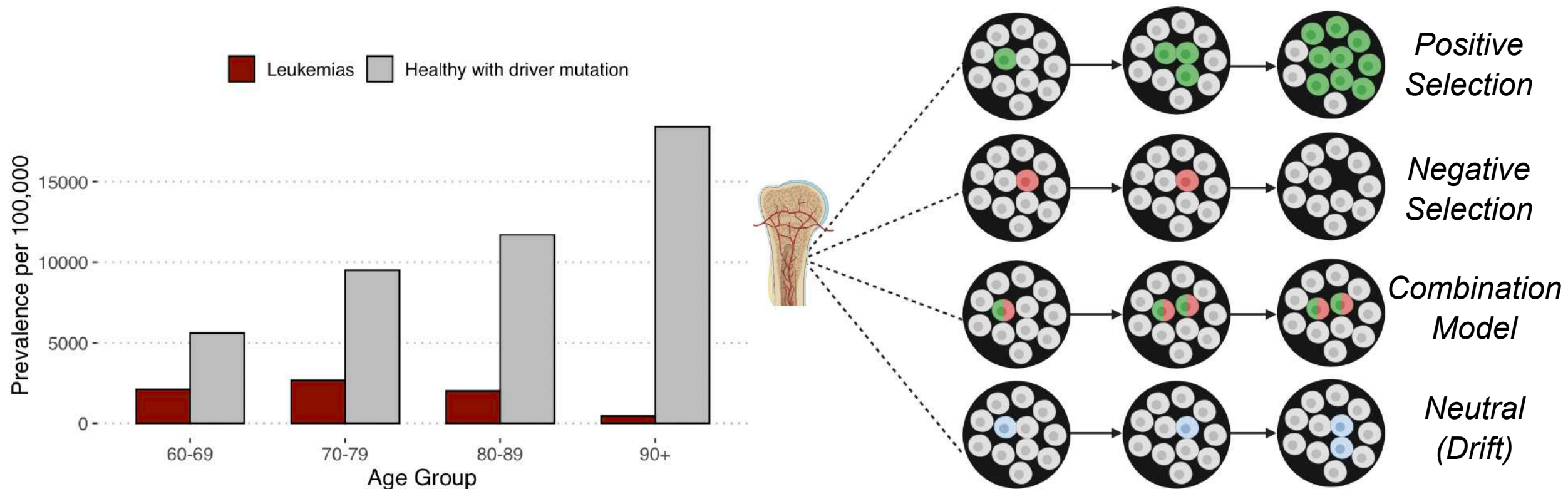
Hernandez et al. 2011, Hussin et al. 2015

Mutations in driver genes are common in healthy individuals



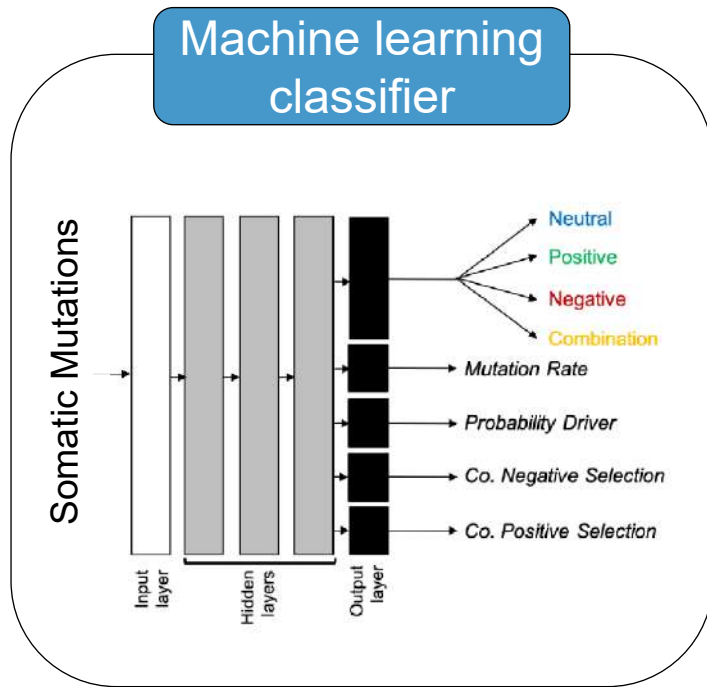
McFarland et al. 2013

Mutations in driver genes are common in healthy individuals



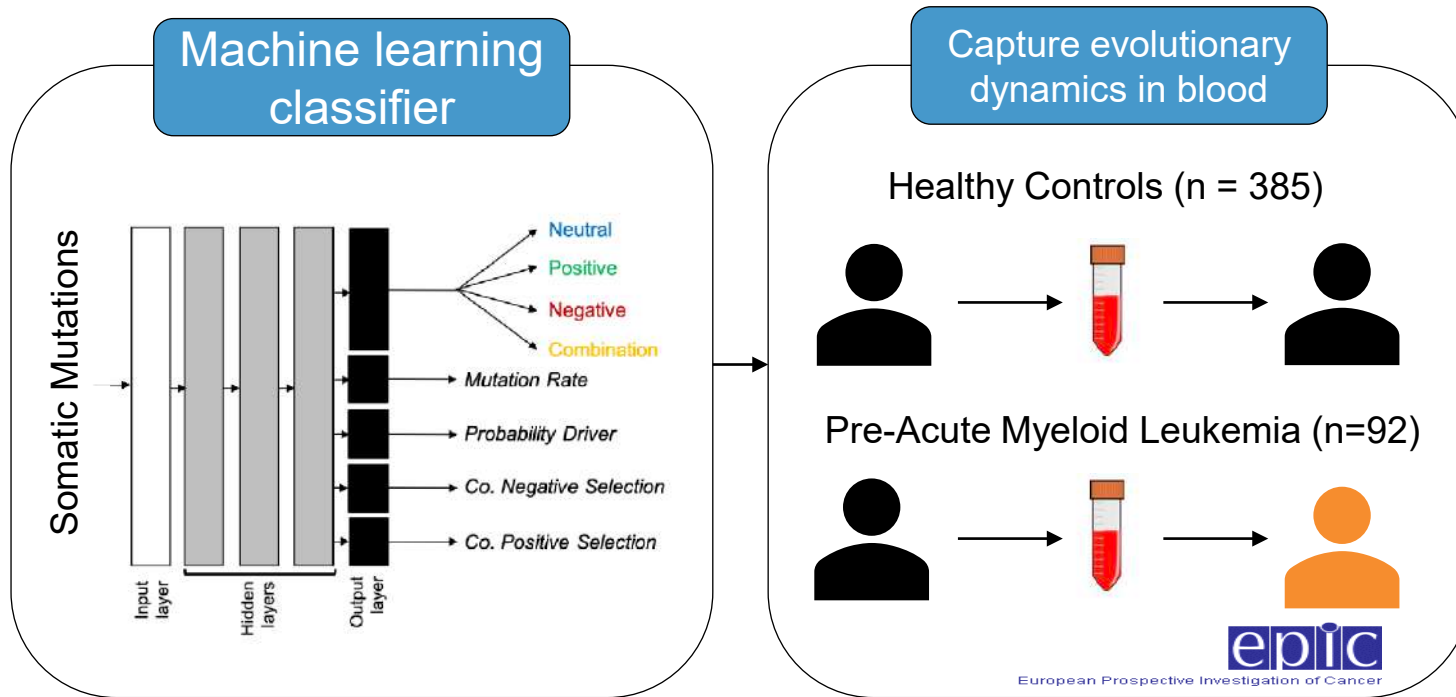
Kimura (1983), Zink et al. (2017), Lee Six et al. (2018)

Interacting evolutionary pressures in blood shape health outcomes as we age



Skead, K. et al. Nature Communications (2021)

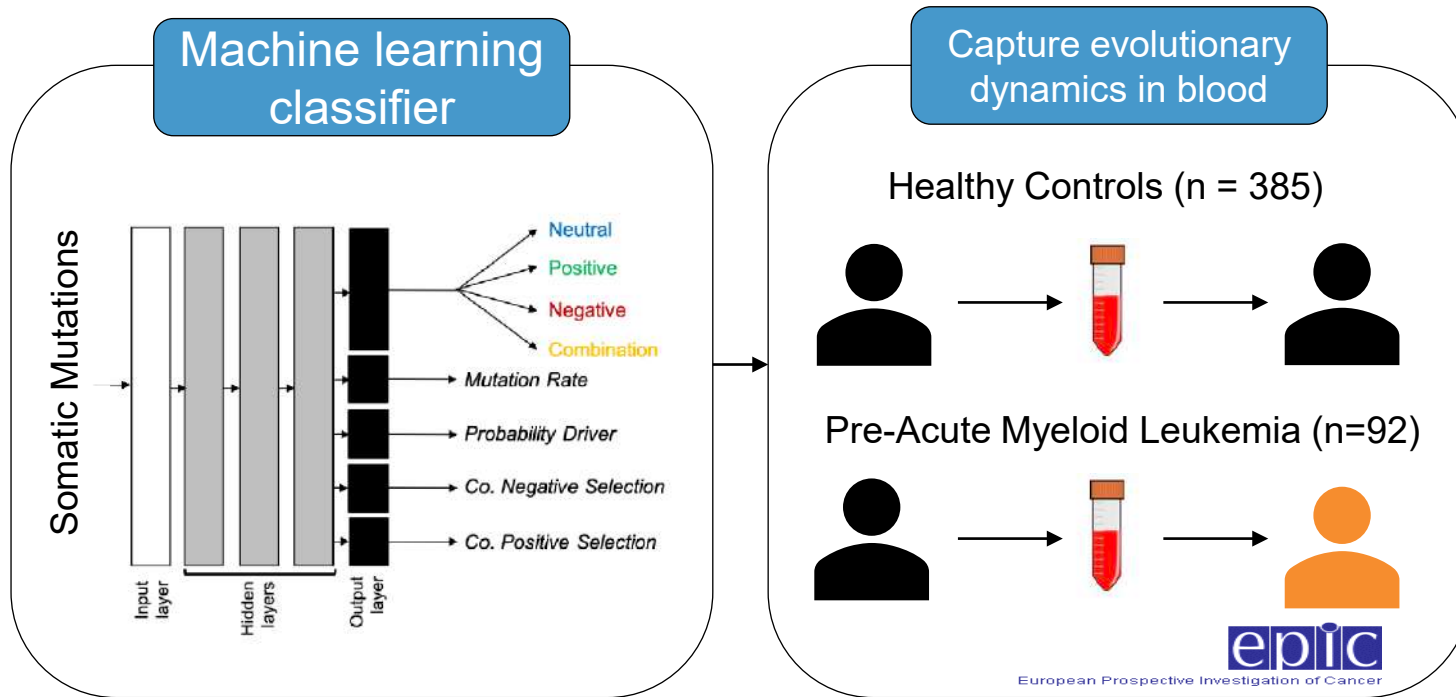
Interacting evolutionary pressures in blood shape health outcomes as we age



Abelson S, et al. Nature 2018

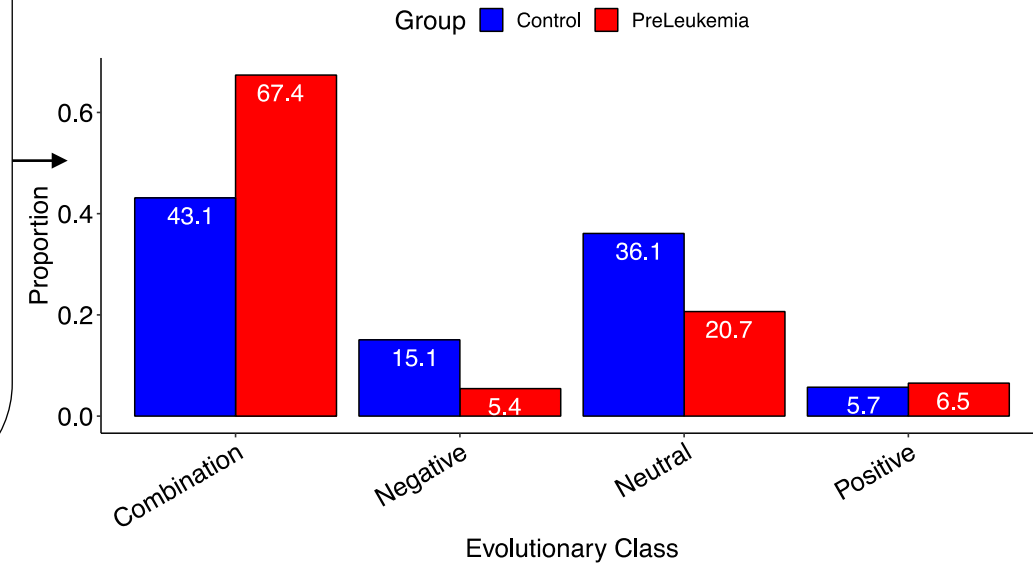
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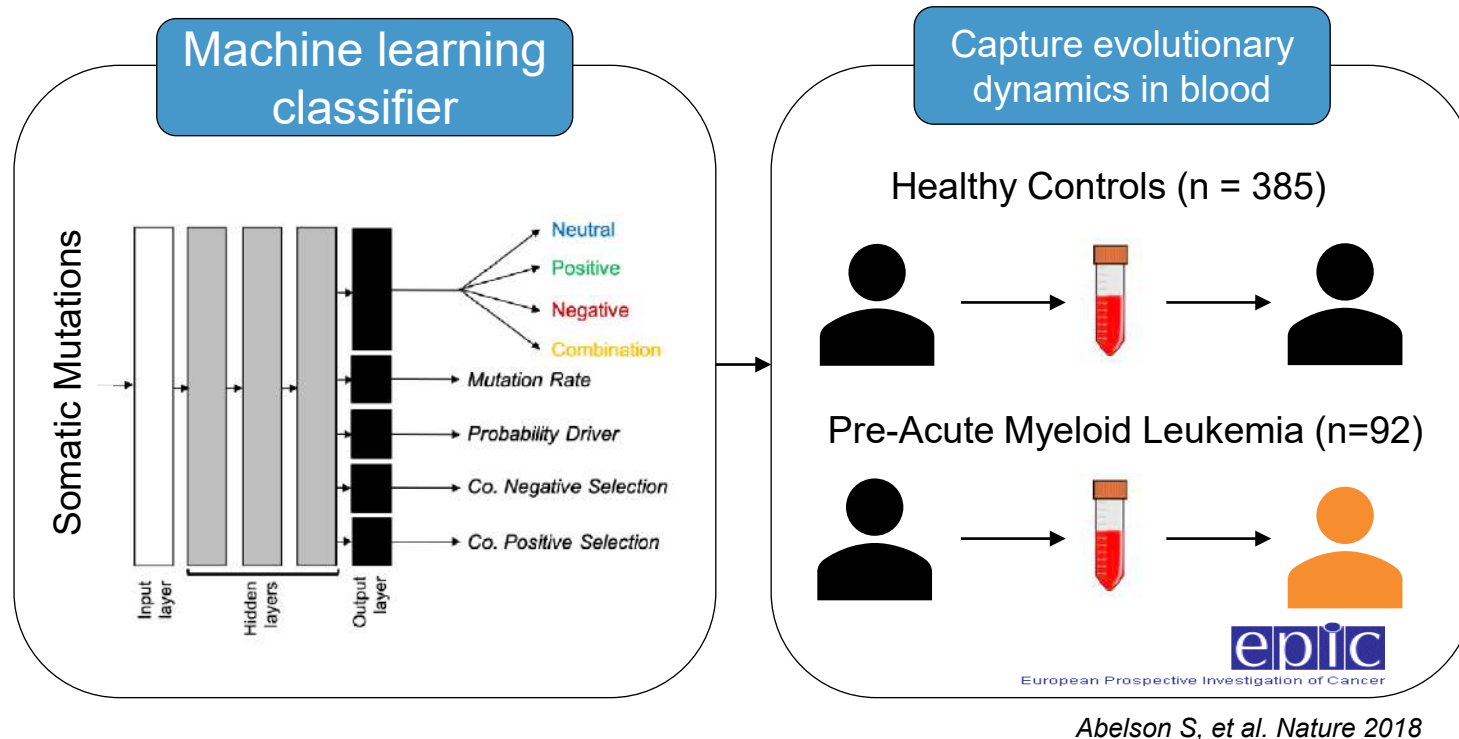
Abelson S, et al. Nature 2018

Most individuals reject positive-only or neutral models of evolution

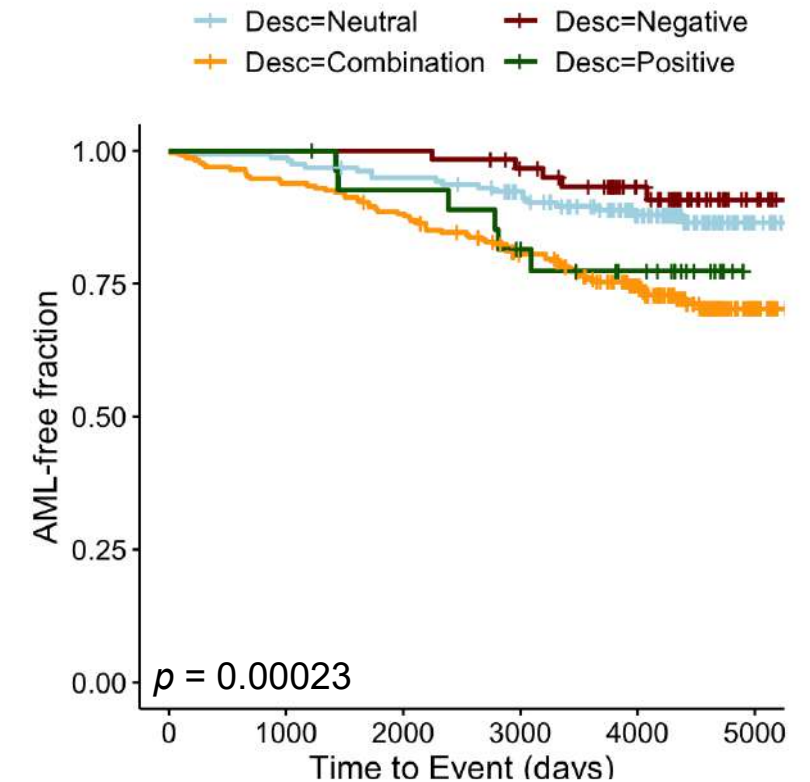


Skead, K. et al. Nature Communications (2021)

Interacting evolutionary pressures in blood shape health outcomes as we age



Negative selection is associated with longer AML-free survival



Skead, K. et al. Nature Communications (2021)

Why are large mutations tolerated in our blood?

Insights into clonal haematopoiesis from 8,342 mosaic chromosomal alterations

[Po-Ru Loh](#) ✉, [Giulio Genovese](#) ✉, [Robert E. Handsaker](#), [Hilary K. Finucane](#), [Yakir A. Reshef](#), [Pier Francesco Palamara](#), [Brenda M. Birman](#), [Michael E. Talkowski](#), [Samuel F. Bakhoun](#), [Steven A. McCarroll](#) ✉ & [Alkes L. Price](#) ✉

[Nature](#) **559**, 350–355 (2018) | [Cite this article](#)

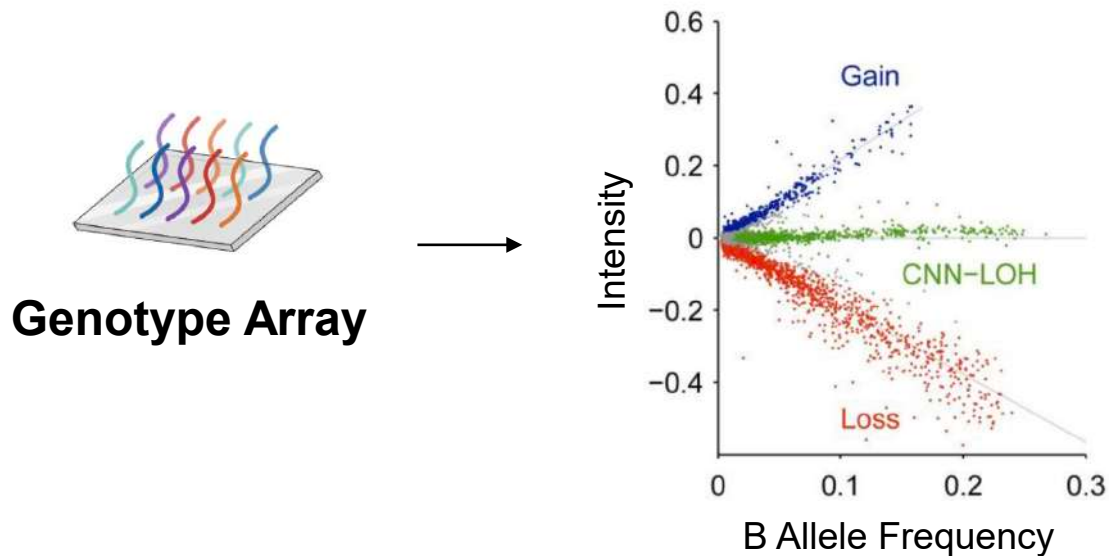


Figure adapted from Loh, P. et al. 2018

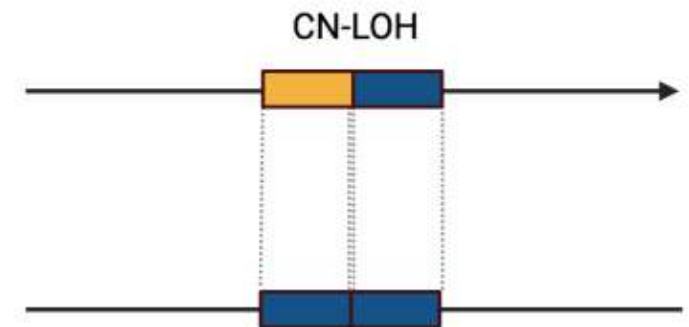
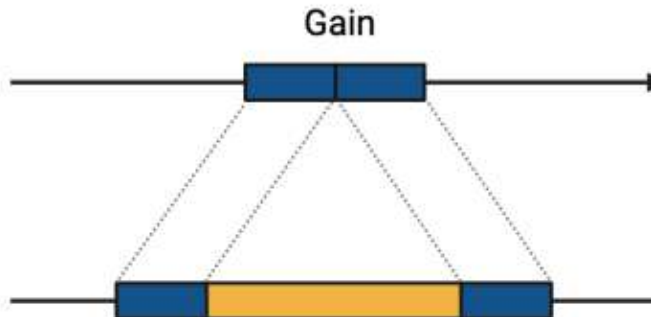
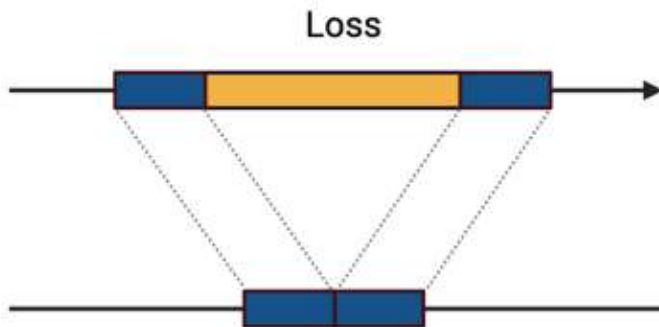
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- Mosaic chromosomal alterations (mCAs) were found in approximately **5% of the population**



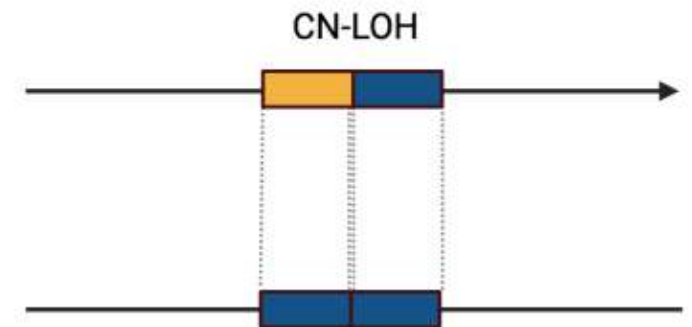
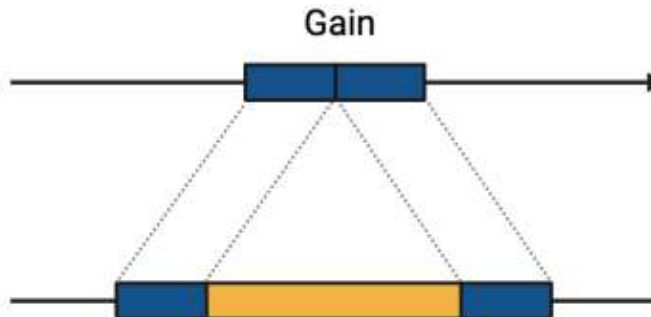
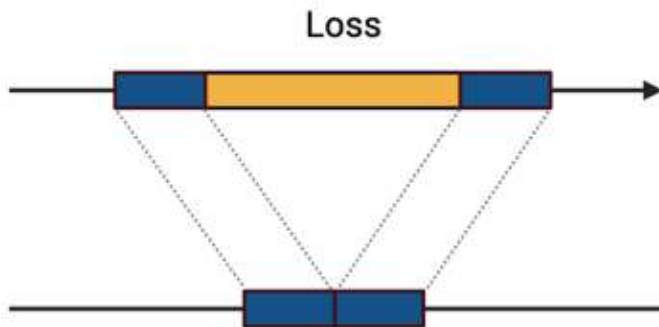
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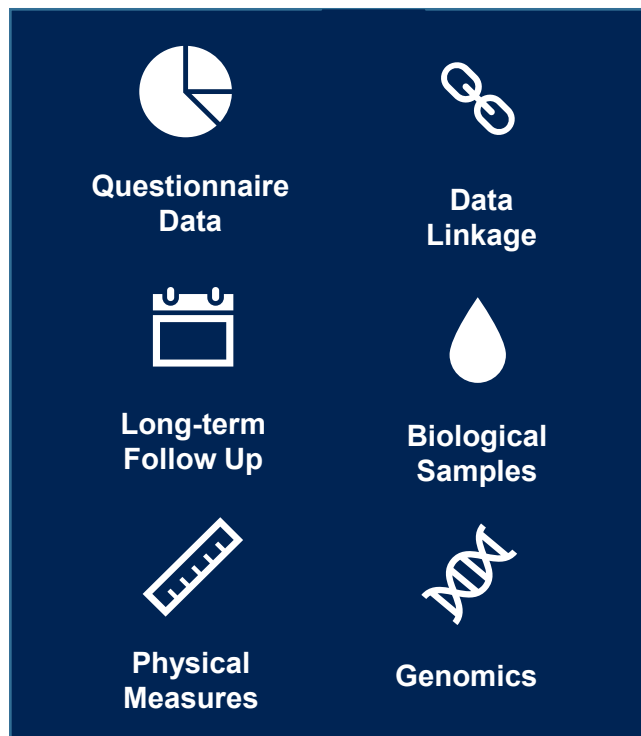
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- Mosaic chromosomal alterations (mCAs) were found in approximately **5% of the population**
- If **selection is playing a role in maintaining somatic mutations in blood, why are large mCAs tolerated?**



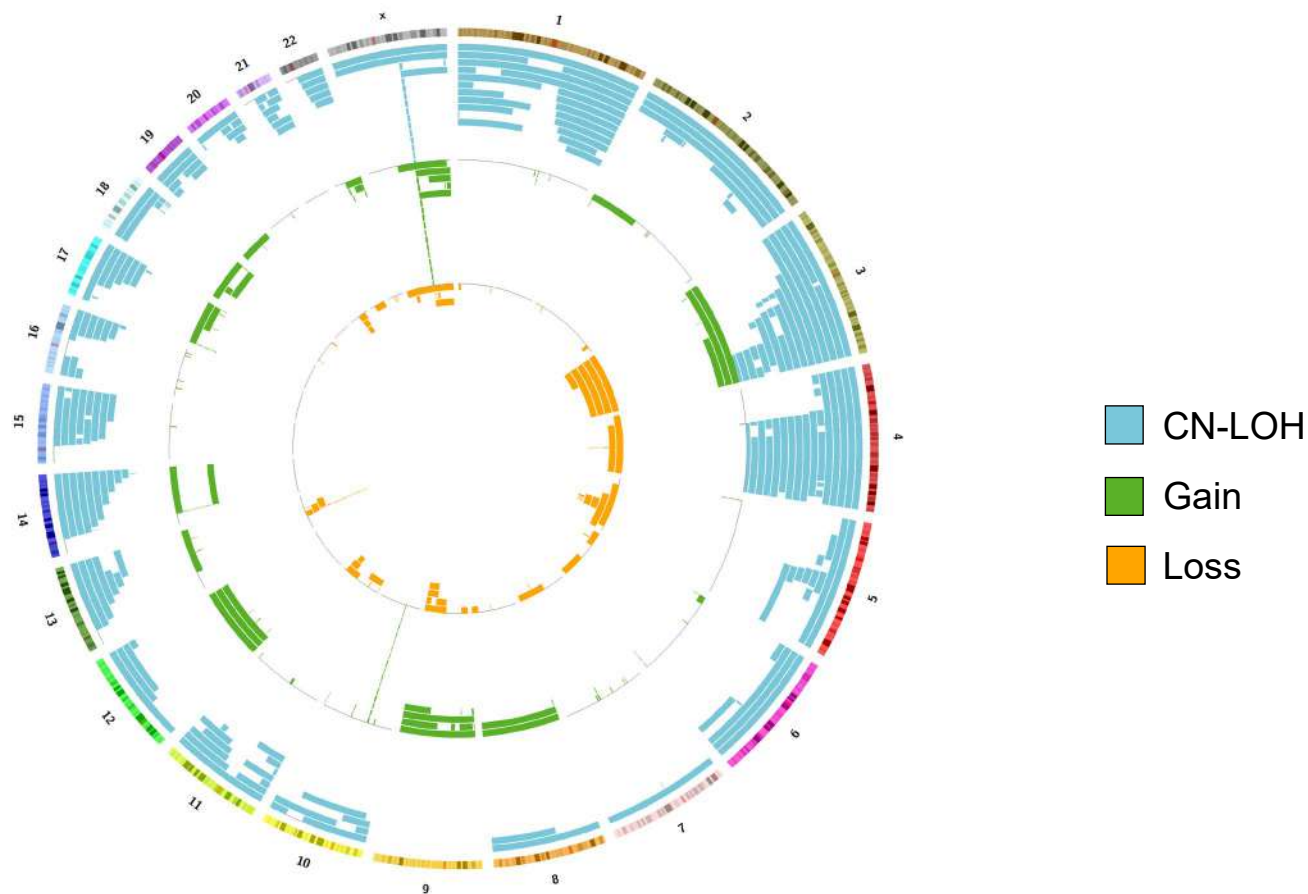
Capturing somatic mosaicism in the Canadian population

CanPath is a population-health research platform built to assess the effect of genetics, behavior, health history and environment on chronic diseases.



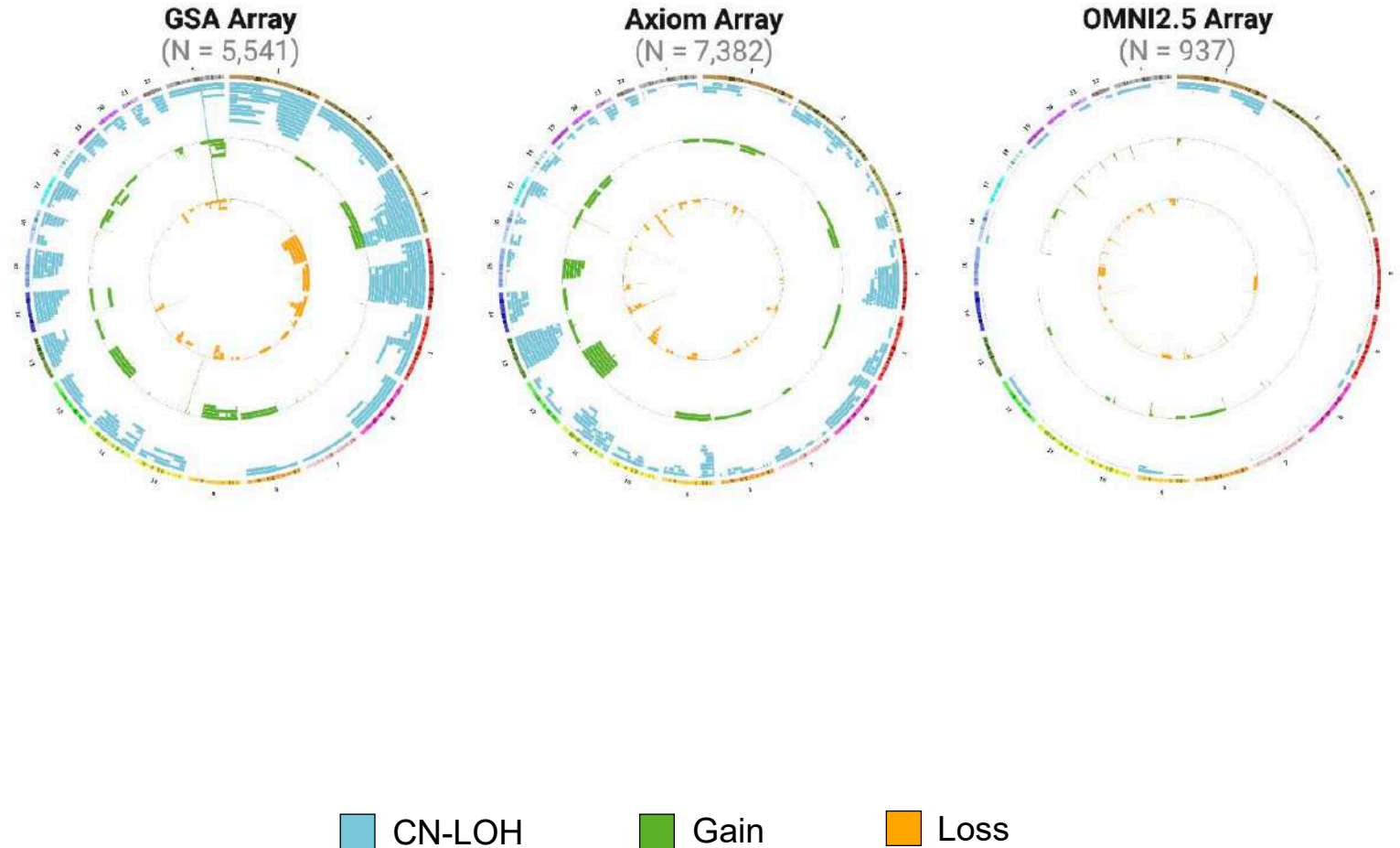
ARCH attributable to mosaic chromosomal alterations is three times more common than previously estimated

Mosaic chromosomal alterations were called from genotype array data across ~14,000 individuals



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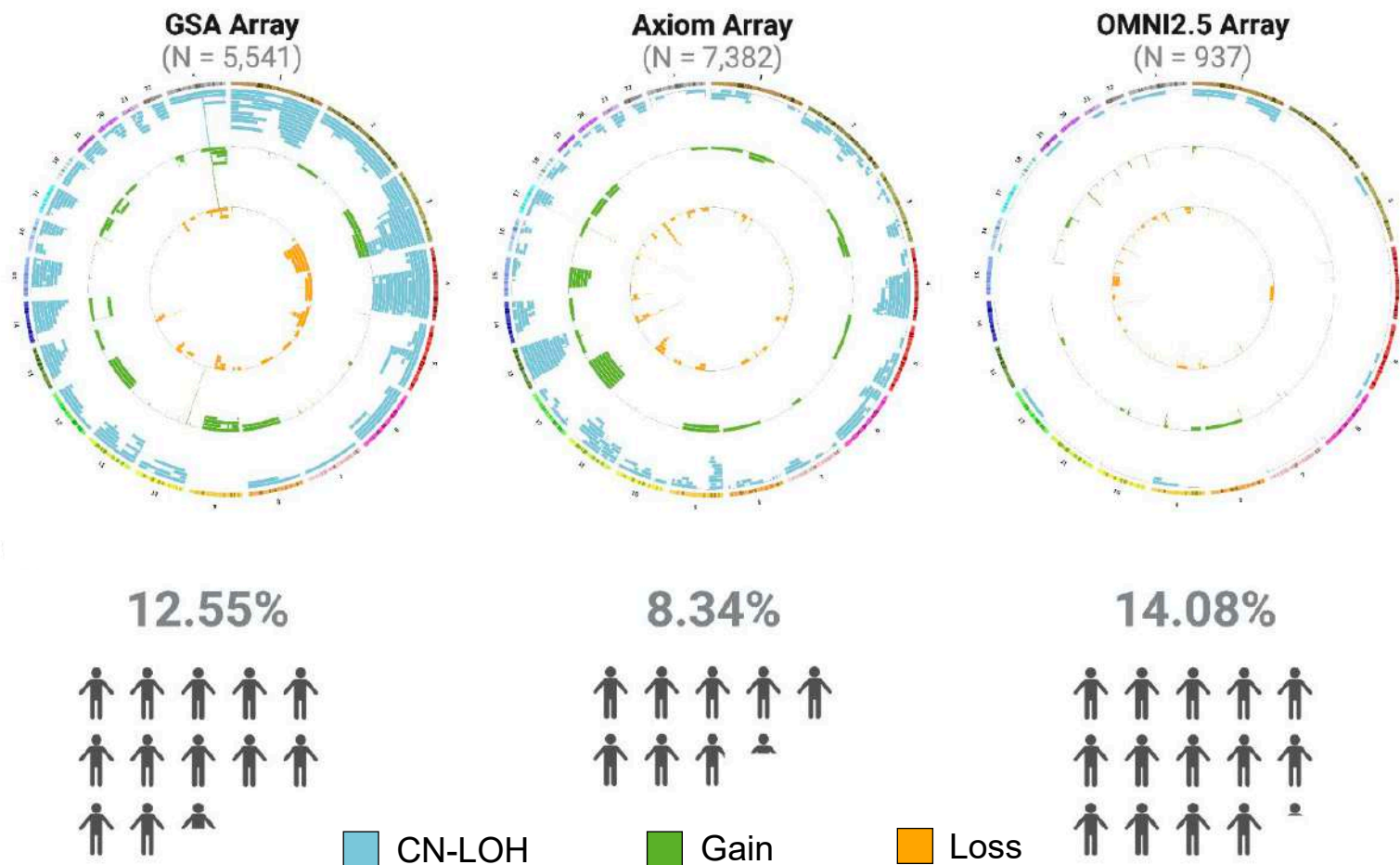
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We capture a higher prevalence of mCAs (3x) than previously reported using denser sequencing arrays

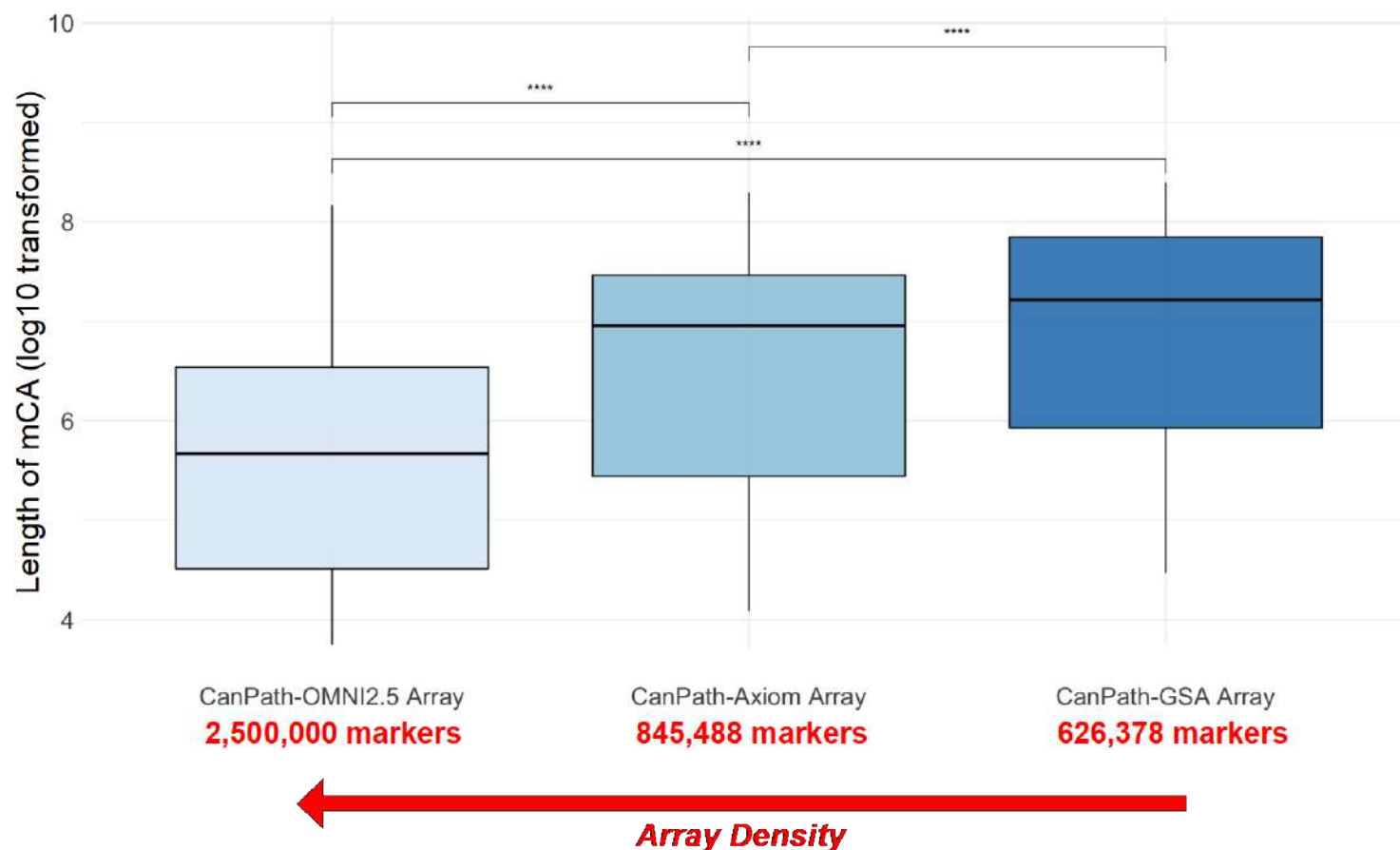


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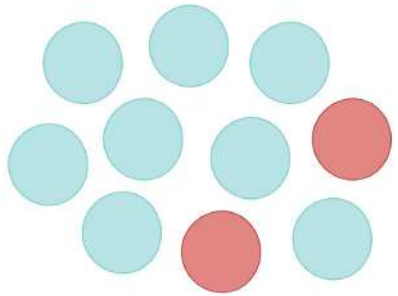
We capture a higher prevalence of mCAs (3x) than previously reported using denser sequencing arrays

Higher density arrays enable us to detect smaller mCAs that were previously missed

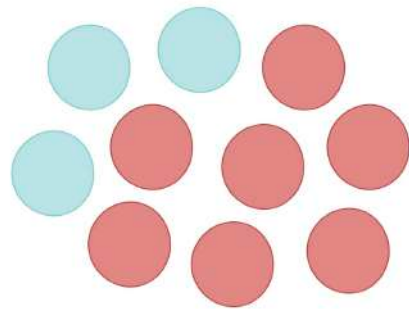


Determining the impact of selection on shaping mCA accumulation in blood

Low cell fraction



High cell fraction

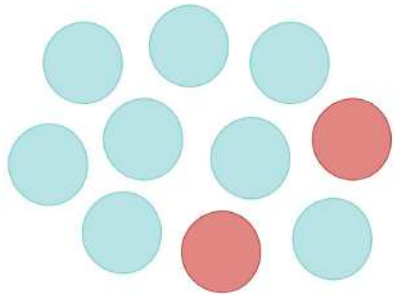


 Cell with mCA

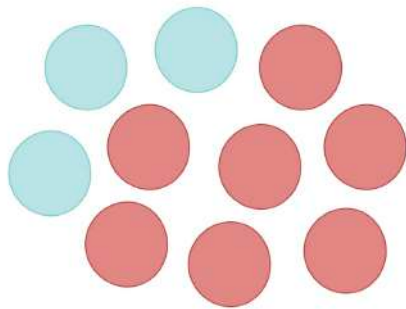
 Cell with no mCA

Determining the impact of selection on shaping mCA accumulation in blood

Low cell fraction



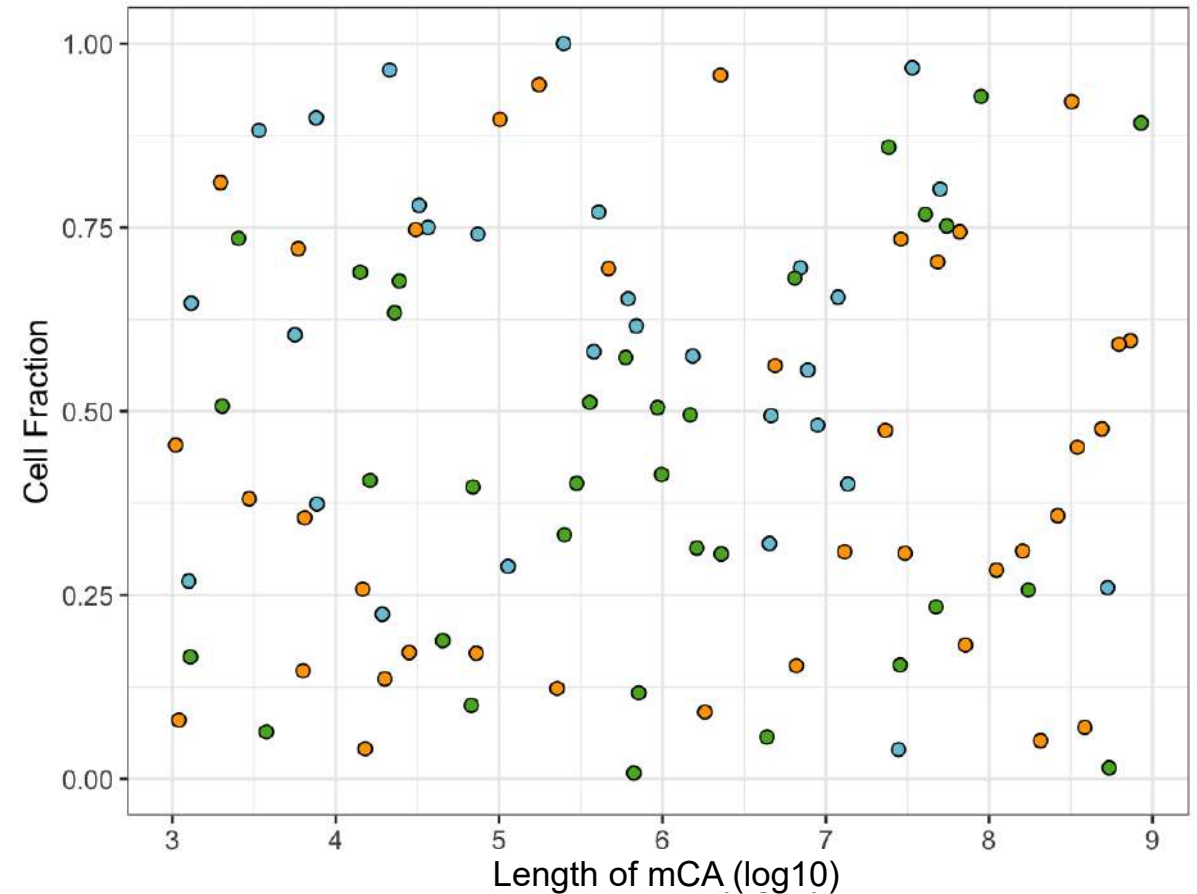
High cell fraction



 Cell with mCA

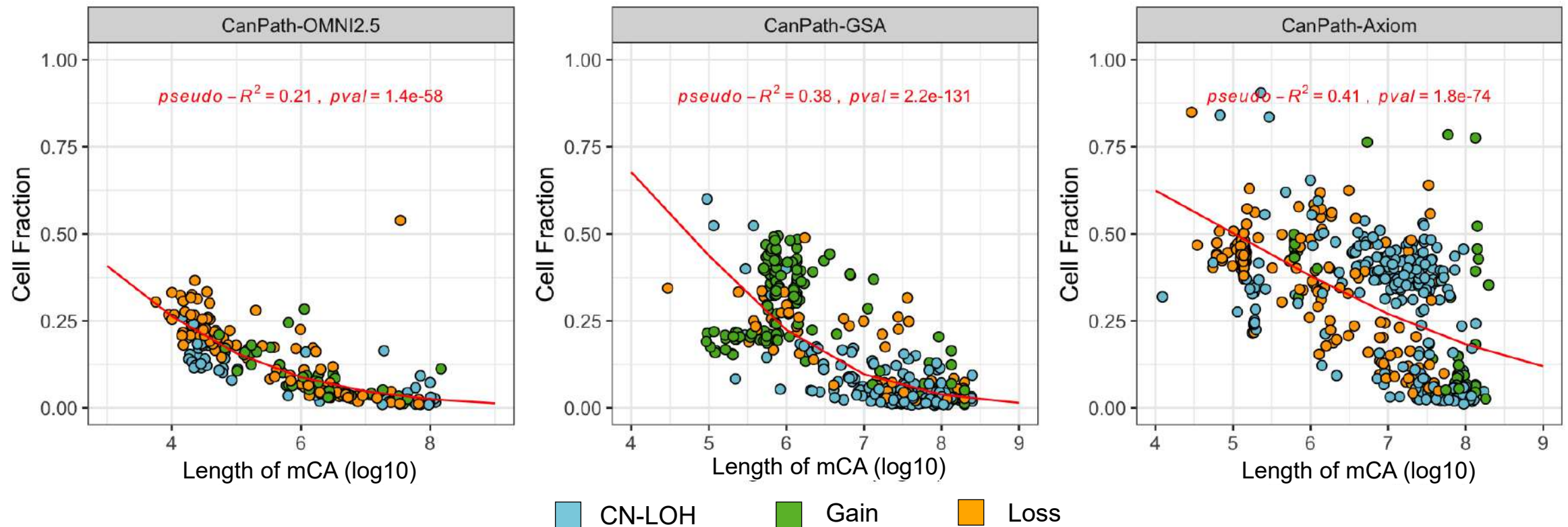
 Cell with no mCA

Under a **neutral model of evolution**, we would **not expect to see an association** between the frequency of a mCA and the size of a mCA

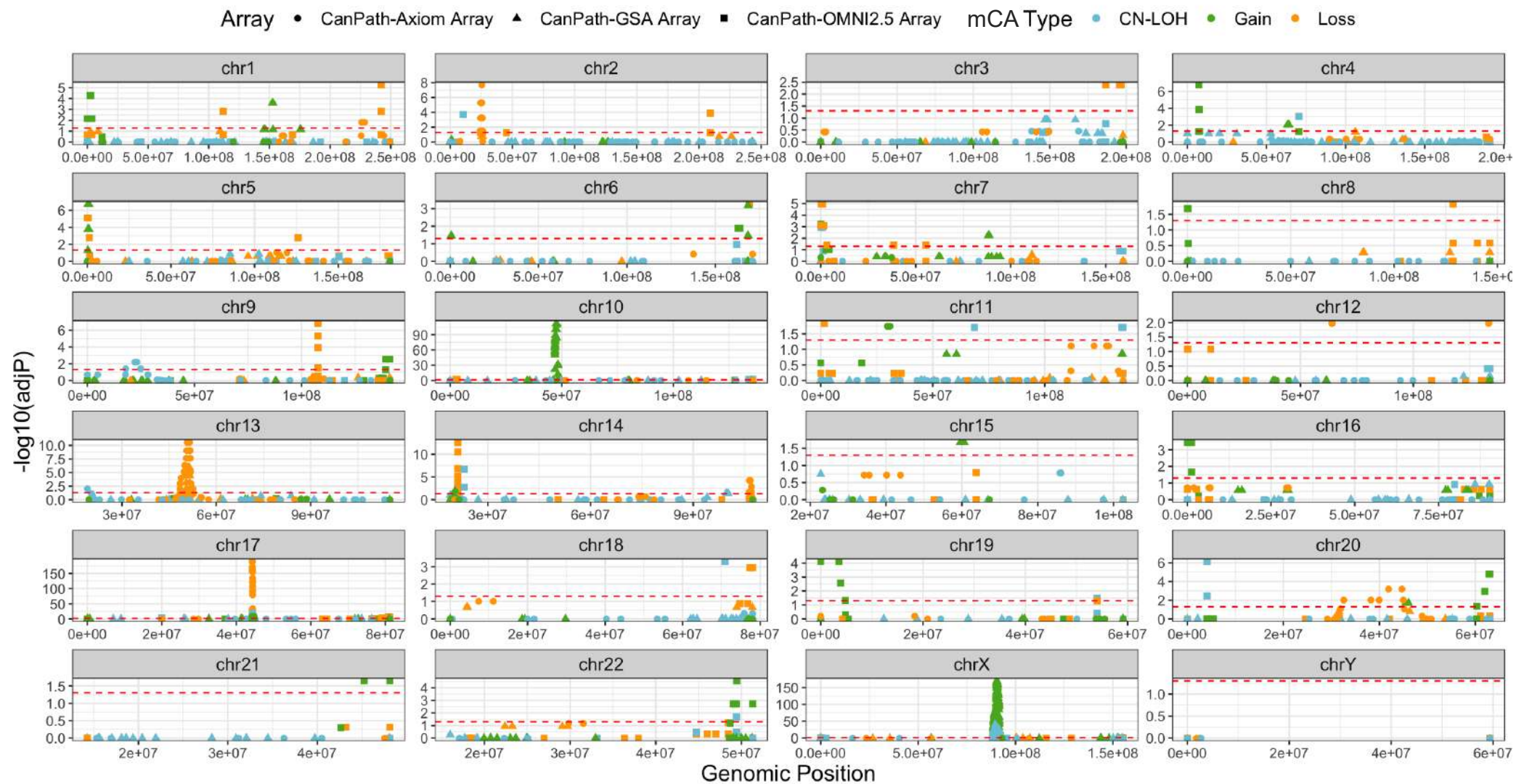


Large mosaic chromosomal alterations are observed at low frequencies in the hematopoietic pool

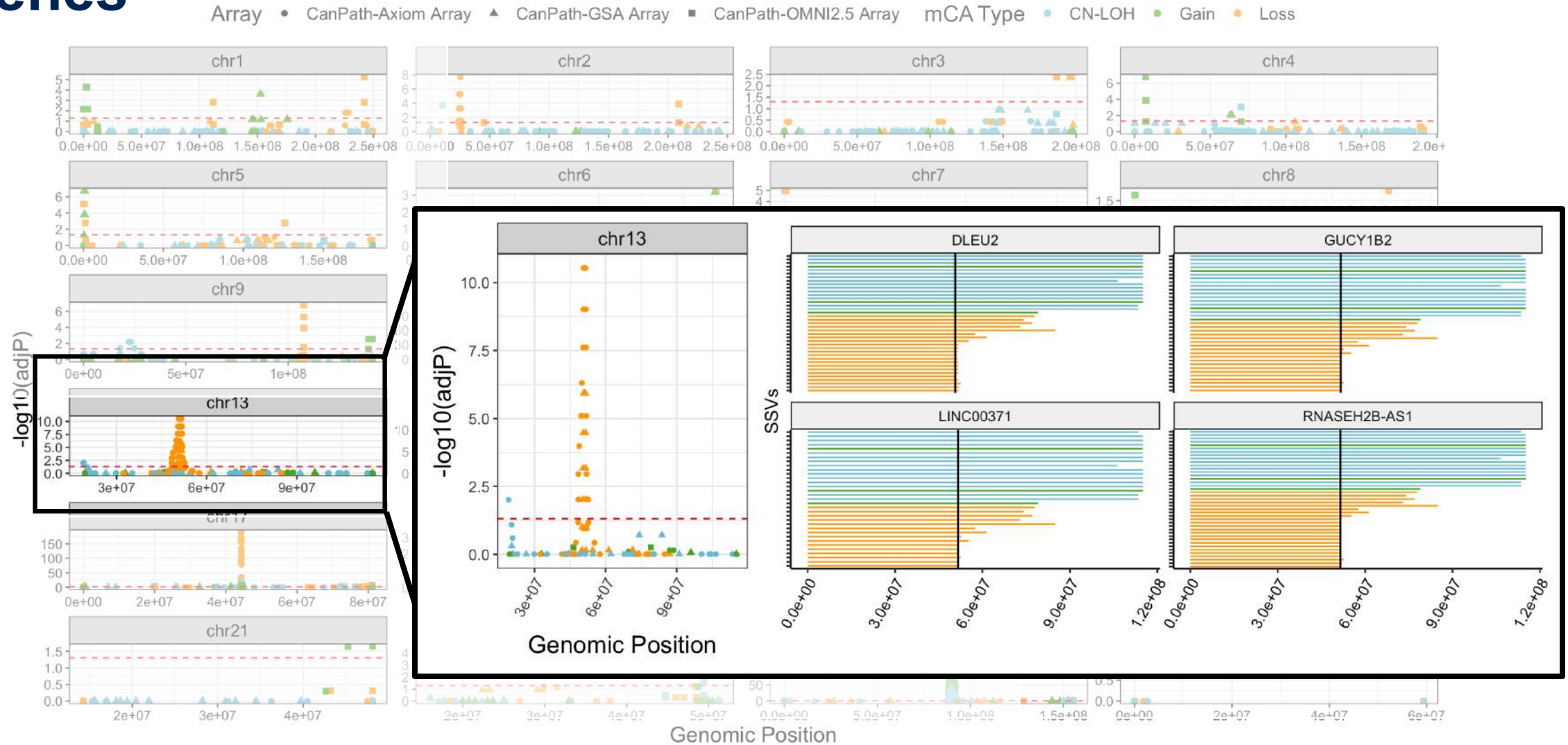
- The size of mCAs impact the frequency at which they segregate in our blood
- **Negative selection plays a role in removing large mCAs** from the hematopoietic population



Genome-wide hotspotting approach detects regions which harbour a high burden of mosaic chromosomal alterations



mCAs accumulate across ARCH- and cancer-associated genes

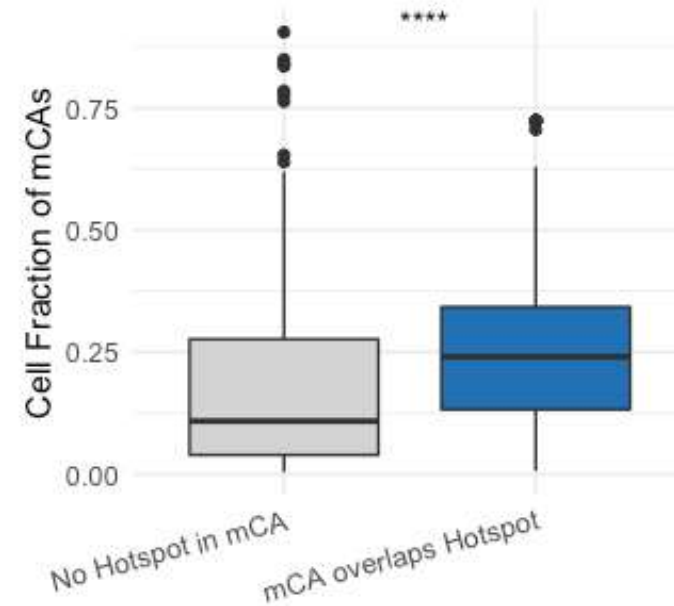


mCAs accumulate across ARCH- and cancer-associated genes



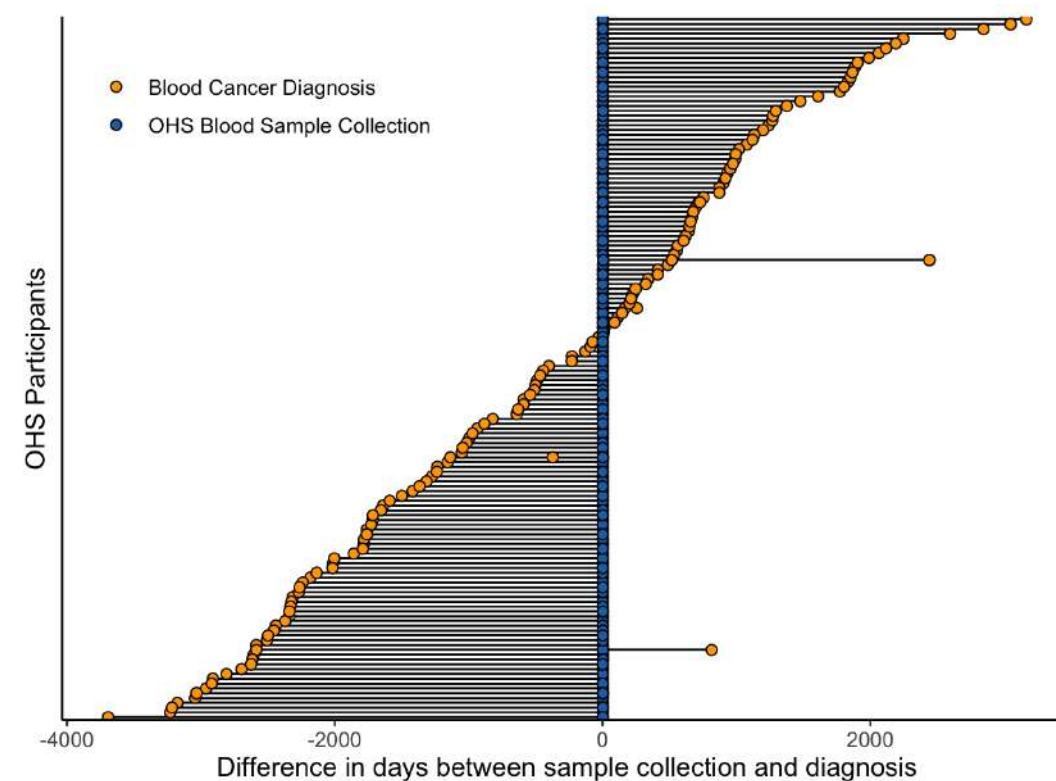
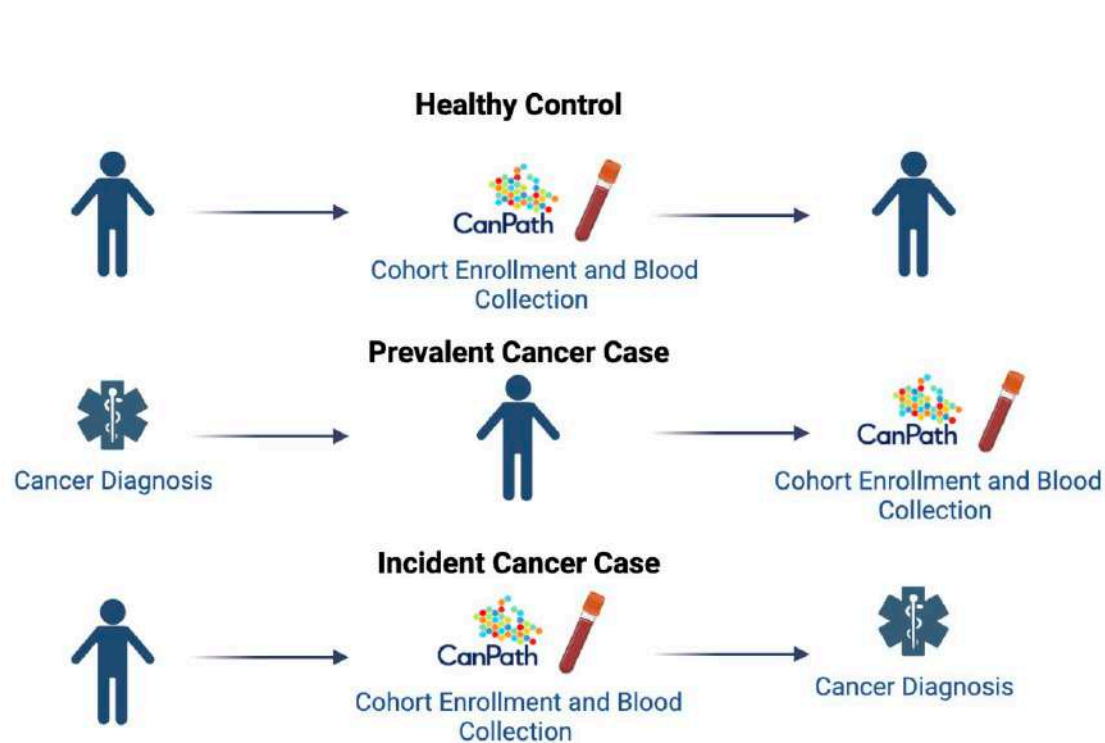
mCA hotspots suggest positive selection is shaping mCA retention and frequencies across the genome

- mCAs accumulate across ARCH- and cancer-associated genes
- mCAs which overlap at least one hotspot are at a significantly higher cell fraction than mCAs which do not overlap hotspots
- Positive selection may be retaining cell fractions at higher frequencies at select regions of the genome



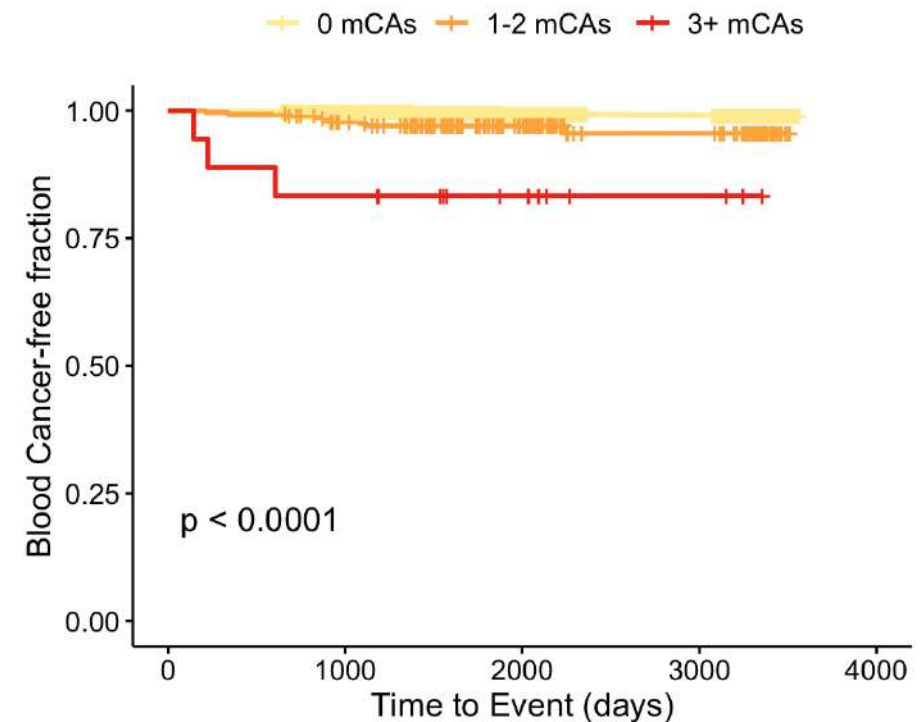
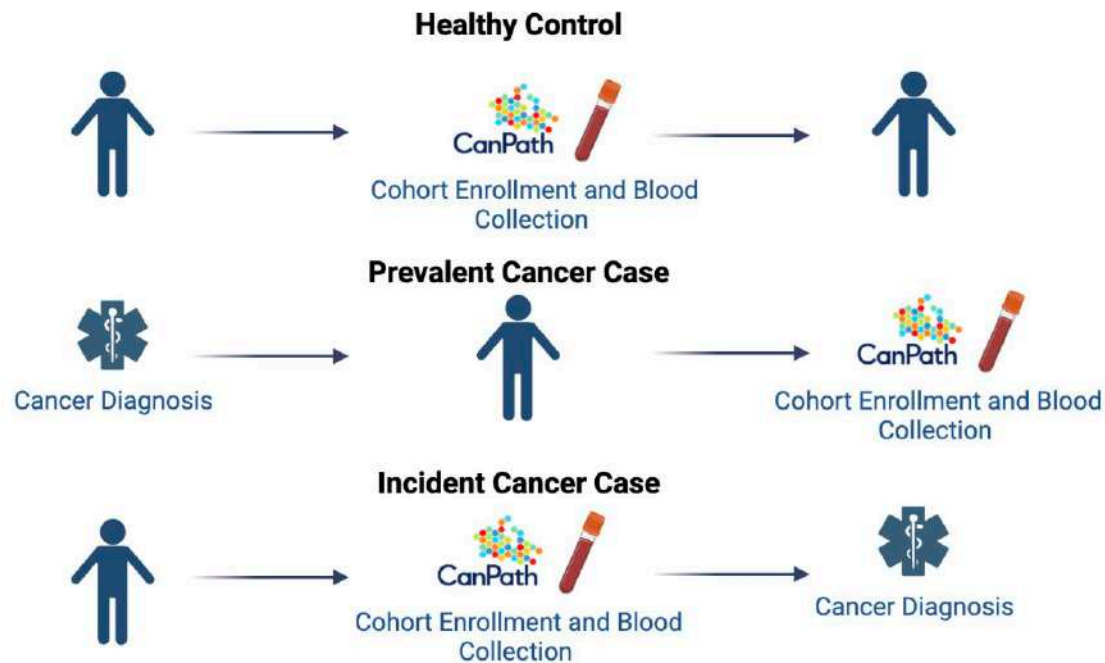
Administrative health linkages enable us to study diseases prior to clinical diagnosis

OHS Pilot: Breast, prostate, pancreatic and hematological malignancies captured through record linkages



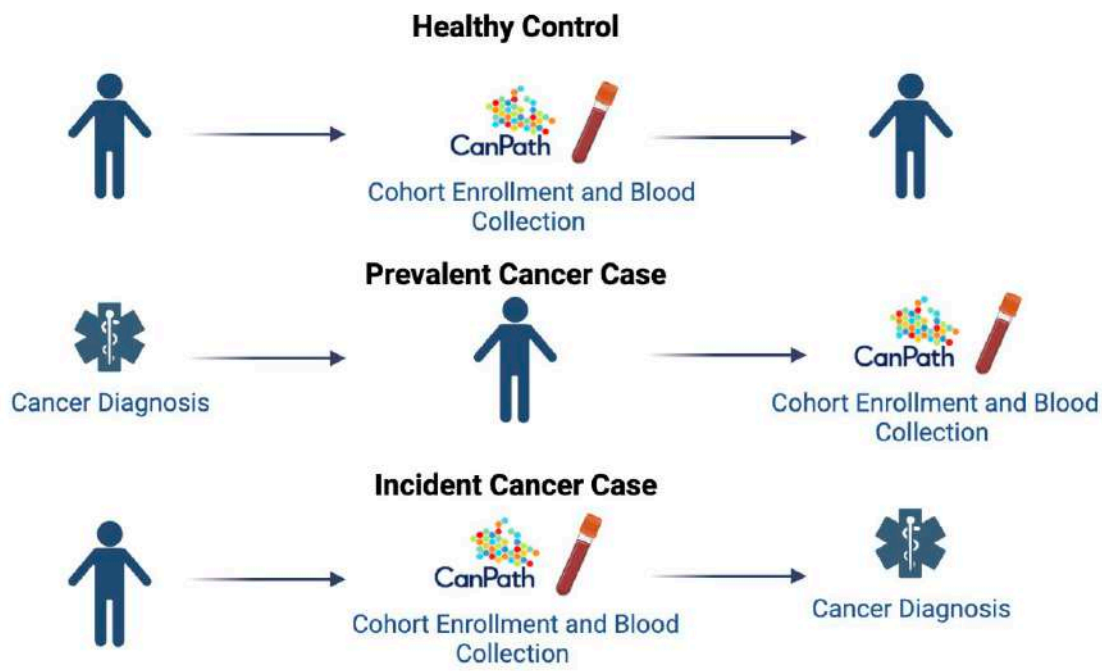
Individuals with at least one mCA are at significantly greater risk of progressing to blood cancer

OHS Pilot: Breast, prostate, pancreatic and hematological malignancies captured through record linkages



Individuals with at least one mCA are at significantly greater risk of progressing to blood cancer

OHS Pilot: Breast, prostate, pancreatic and hematological malignancies captured through record linkages



Variable		N	Hazard ratio		p
Number of mCAs	0	7306	Reference		
	1-2	272	5.06 (2.47, 10.38)		<0.001
	3+	18	26.80 (8.30, 86.56)		<0.001
Age		7596	1.08 (1.04, 1.12)		<0.001
Sex	FEMALE	4721	Reference		
	MALE	2875	2.63 (1.52, 4.56)		<0.001

The Canadian Cancer Study within the Canadian Partnership for Tomorrow's Health



An overview of the
Canadian Partnership for
Tomorrow's Health



Mapping cancer cases in
CanPath with linkages



Using CanPath to identify
the earliest events in
cancer evolution

Accessing CanPath Data

<https://portal.canpath.ca/?&language=fr>



Portail CanPath

Le portail du partenariat canadien pour la santé de demain (CanPath) offre aux chercheurs des outils permettant d'identifier les données et échantillons biologiques recueillis par les six cohortes participantes afin de répondre à de nombreuses questions de recherche novatrices. Une demande d'accès aux données peut être initiée directement à partir du portail.



Cohorte



Pour en savoir plus sur les six cohortes régionales de CanPath.

[En savoir plus](#)

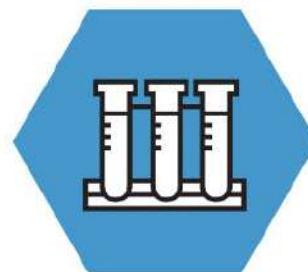
Données



Pour en savoir plus sur les ensembles de données de CanPath et l'approche d'harmonisation des données.

[En savoir plus](#)

Échantillons



Pour en savoir plus sur les échantillons biologiques de CanPath et leur disponibilité.

[En savoir plus](#)

Accès



Pour en savoir plus sur les politiques et les procédures d'accès au CanPath et sur les projets de recherche approuvés.

[En savoir plus](#)

CanPath - A partnership of leading health institutes from coast to coast



Hosted by:



UNIVERSITY OF TORONTO
DALLA LANA SCHOOL OF PUBLIC HEALTH

In partnership with:



National Funder:



Regional cohorts:



Hosted by:



Regional Funders:





We thank CanPath participants across Canada who generously donate their time, information, and biological samples.

CanPath is a success because of the participants' ongoing commitment.

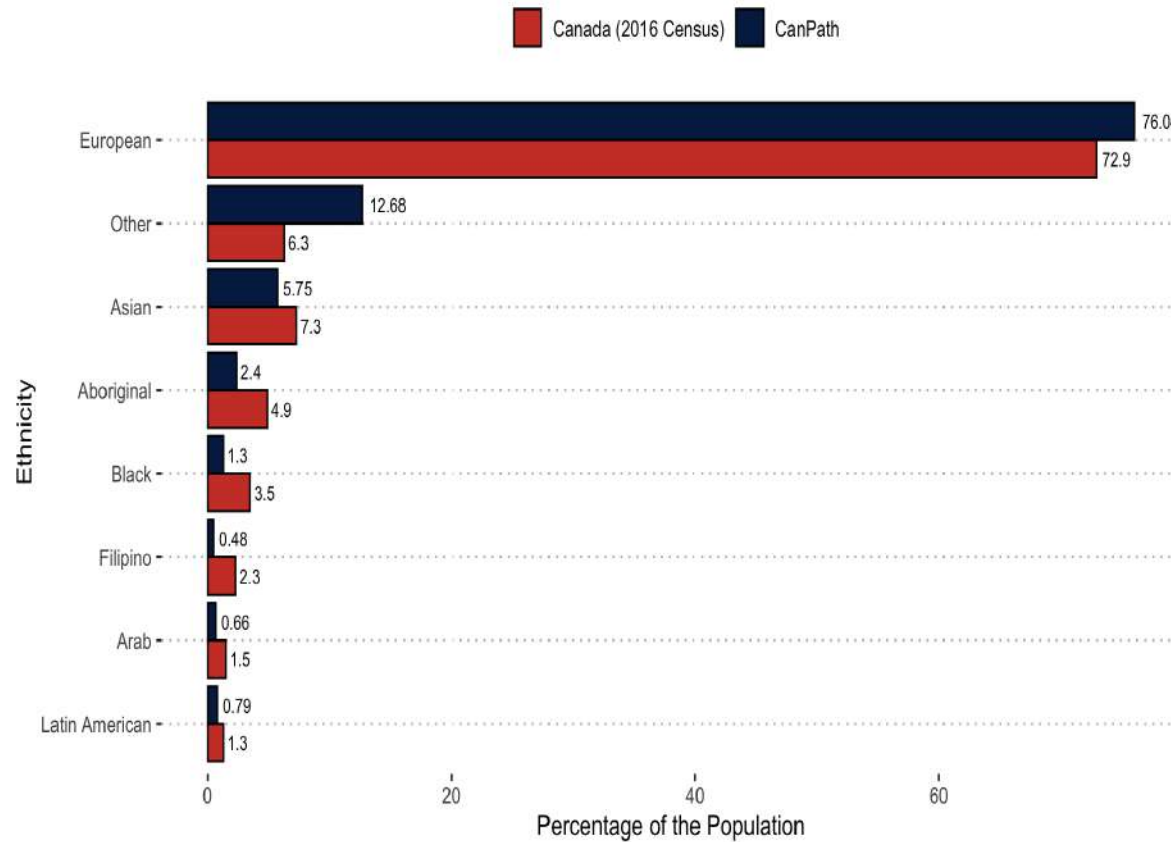
CanPath.ca



CanPath

Canadian Partnership
for Tomorrow's Health

Demographic breakdown of CanPath in relation to Canadian population



CanPath's inclusive recruitment and large size allow the full diversity of the population to be explored, such as racial and ethnic minorities, and other groups who are often under-represented in research.

Priority populations included in COVID-19 initiative (n=20,000)



High prevalence regions



Newcomers to Canada



Long term care residents