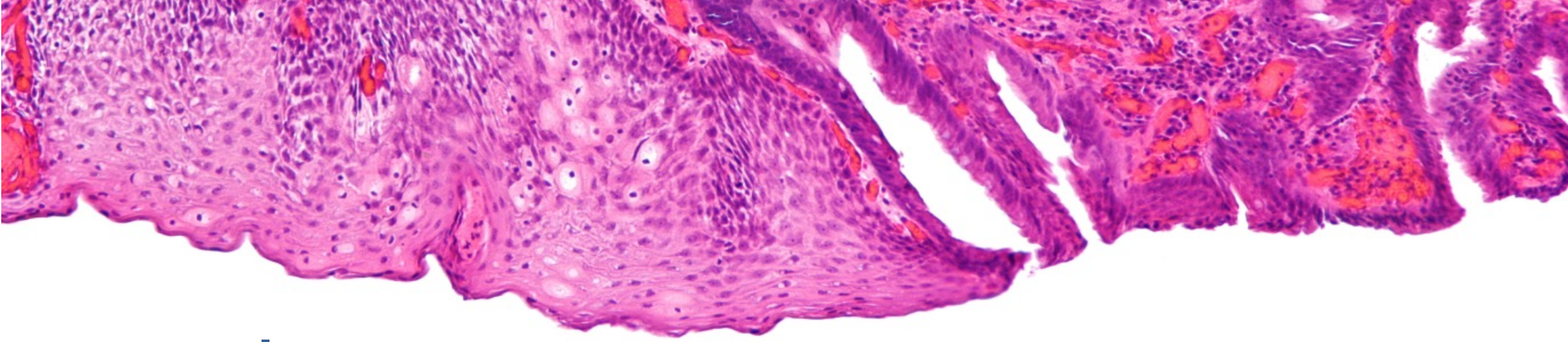
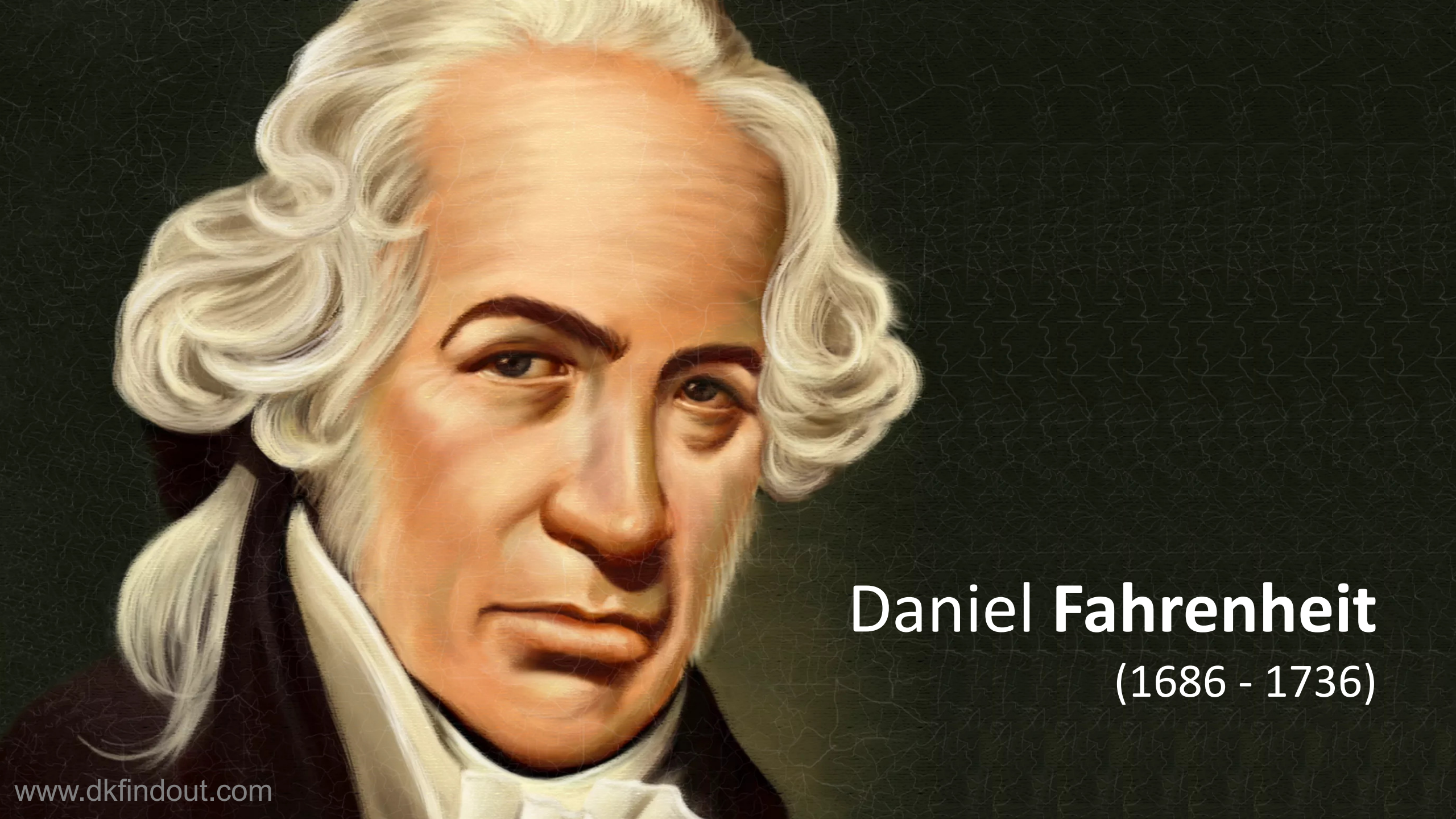


Finding patterns in images and genomes with AI

Florian Markowetz

www.markowetzlab.org

@markowetzlab



Daniel **Fahrenheit**

(1686 - 1736)

Gina Siddiqui, Scientific American, 1 Oct 2018


Won’t work!


But what
about my job?

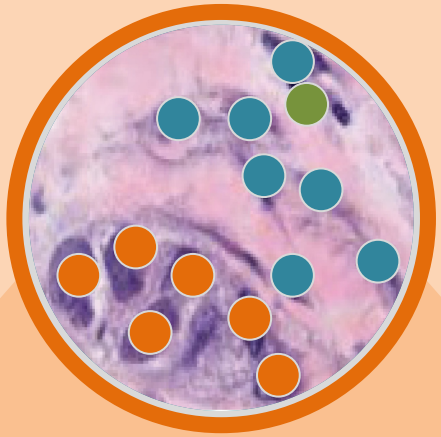
Doctors *with thermometers*
have replaced doctors without

MARKOWETZ LAB
for Integrative Cancer Biology

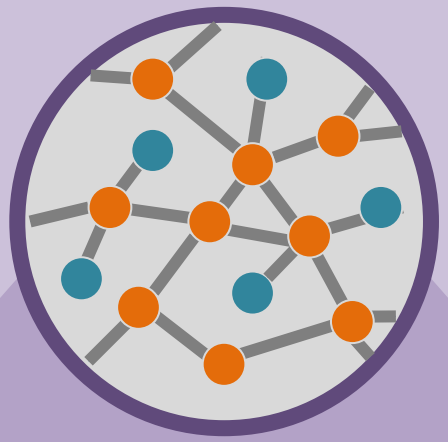
Develop **technologies** for doctors to make **better** decisions **faster**


CANCER RESEARCH UK
CAMBRIDGE INSTITUTE
LMB
AZ
Addenbrookes
Papworth

Genomics of chromosomal instability

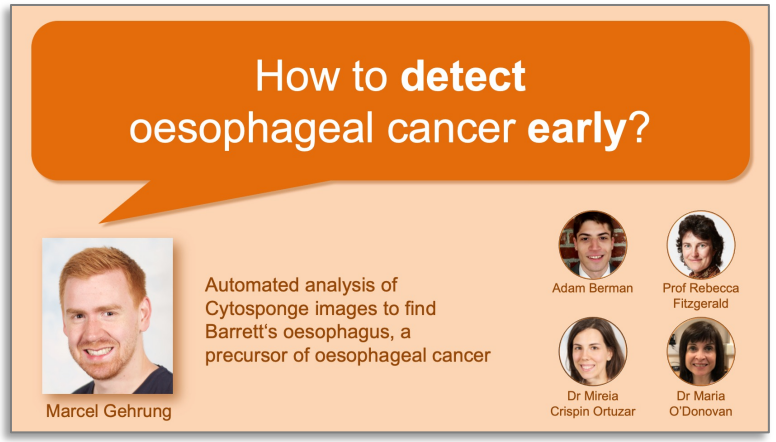


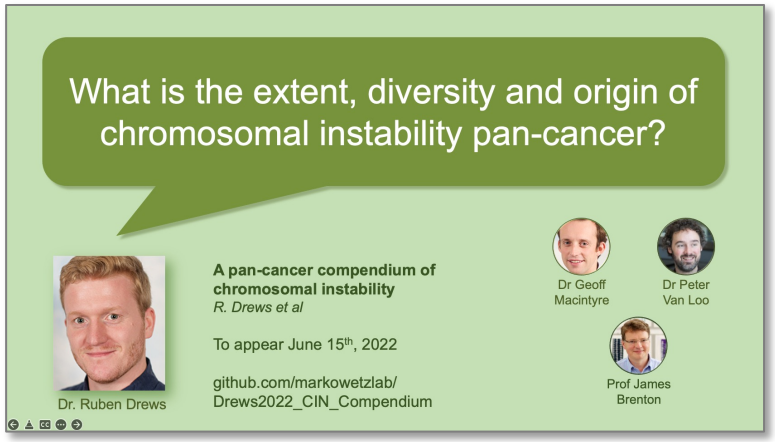
Computational pathology



Perturbation networks

Conflicts of interest





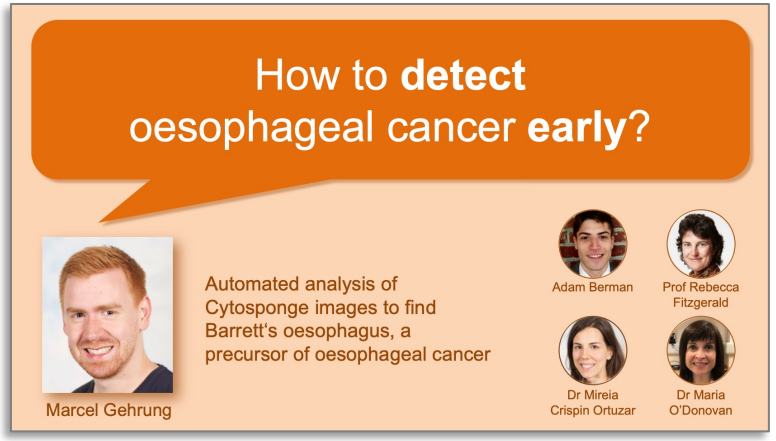
Cyted

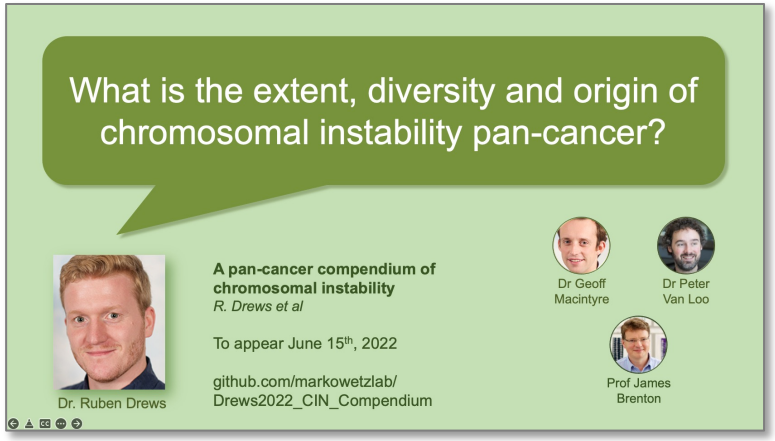
- Based on my lab's research
- CEO was my student

tailor.bio

- Co-founder and director
- Patents and shares

Data and code on **github.com/markowetzlab**





cytosponge-triage (Gehrung 2021)

barretts-segment-length-predictor (Berman 2022)

slidl (Berman 2022)

CNsignatures (Macintyre 2018)

Drews2022 (Drews 2022)

How to detect oesophageal cancer early?

Marcel Gehrung

Triage-driven diagnosis of Barrett's esophagus for early detection of esophageal adenocarcinoma using deep learning

Gehrung et al, 2021

PMID: 33859411

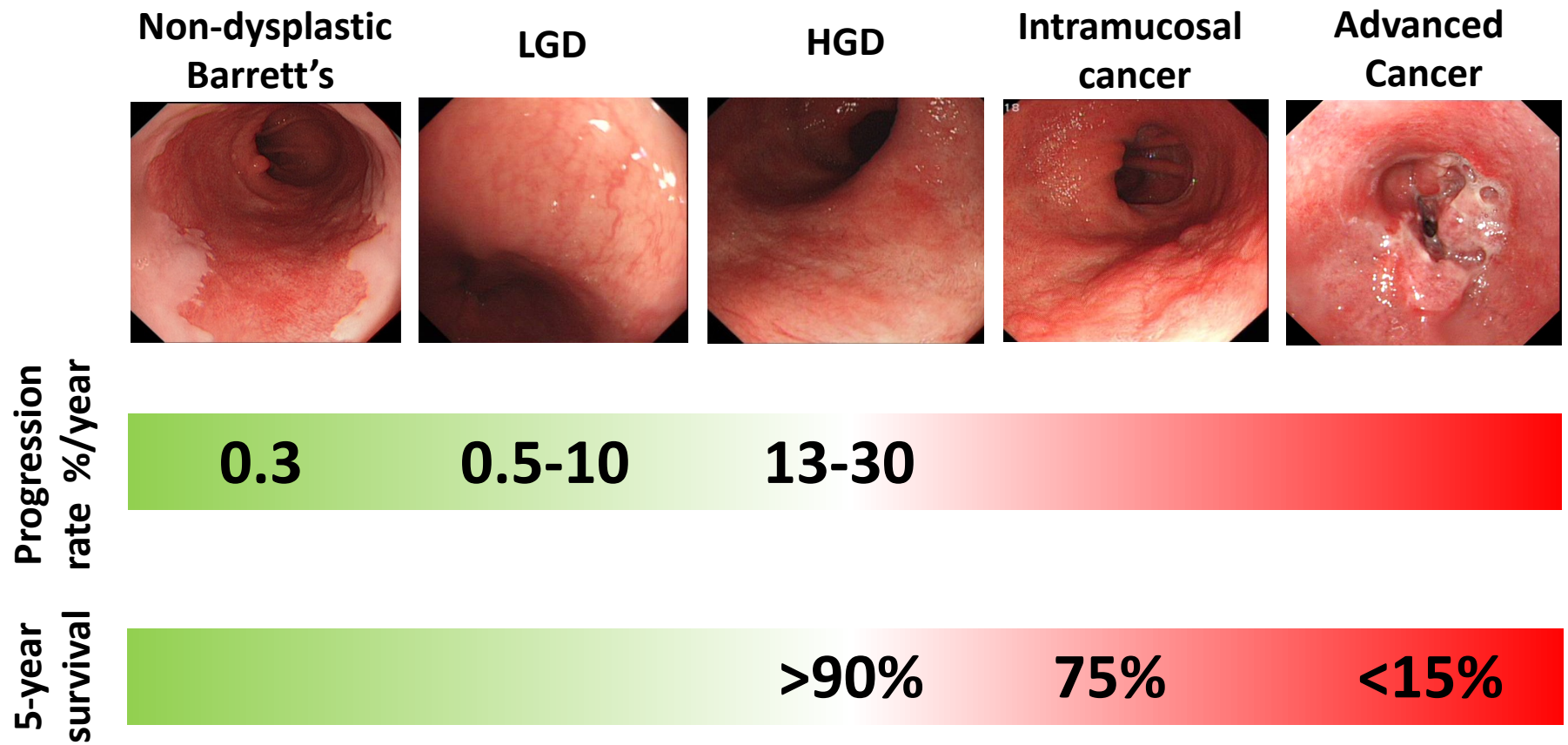
Adam Berman

Prof Rebecca Fitzgerald

Dr Mireia Crispin Ortuzar

Dr Maria O'Donovan

Barrett Oesophagus is a precursor to cancer



Desai Gut 2011, Hvid-Jensen NEJM, 2011, Duits, Gut 2014, Bhat, JNCI 2011

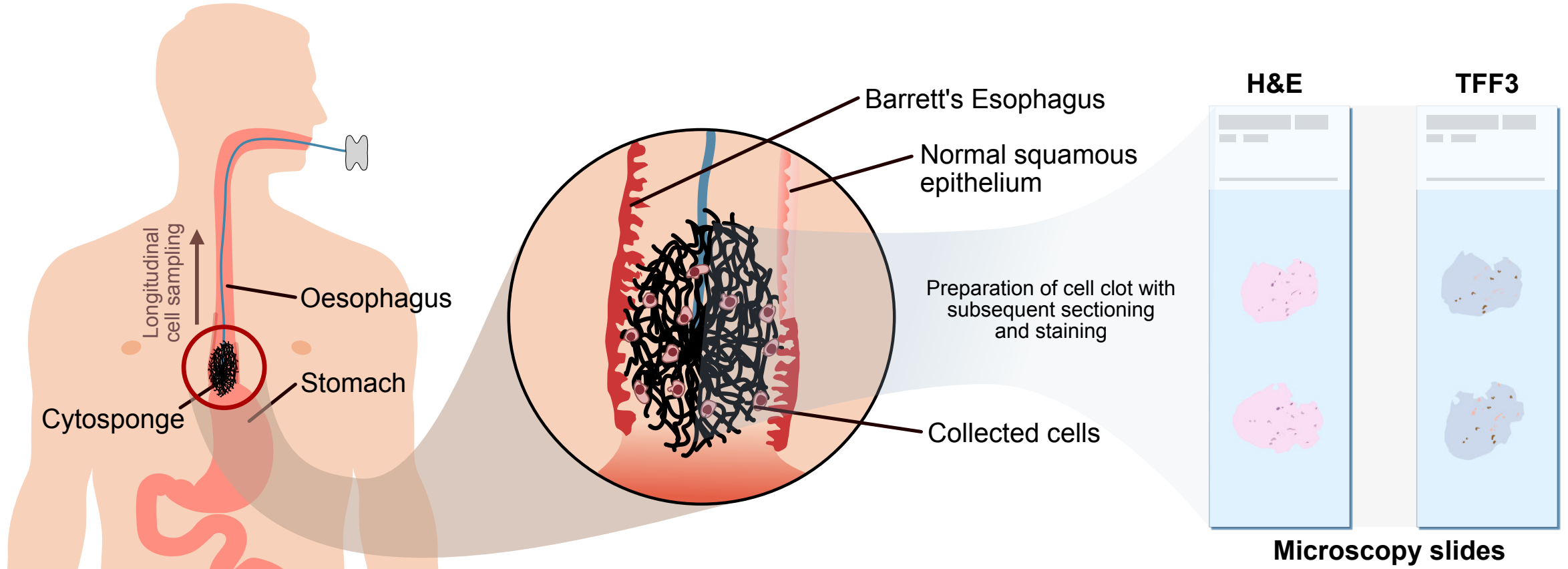
Oesophageal diseases often remain undiagnosed

Referral for endoscopy to investigate heartburn is a barrier for patients and healthcare provider

CYTOSPONGE

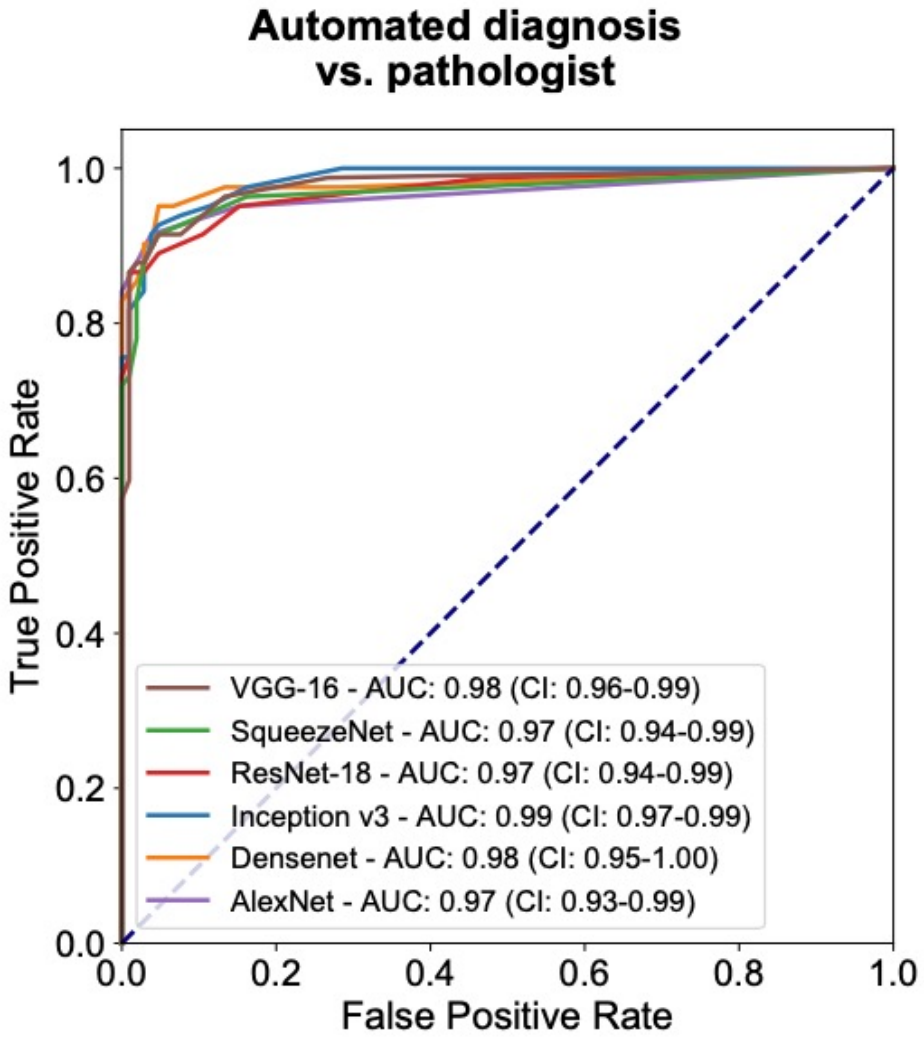
BEST1: Kadri et al 2010
BEST2: Ross-Innes et al 2015
BEST3: Fitzgerald et al 2020

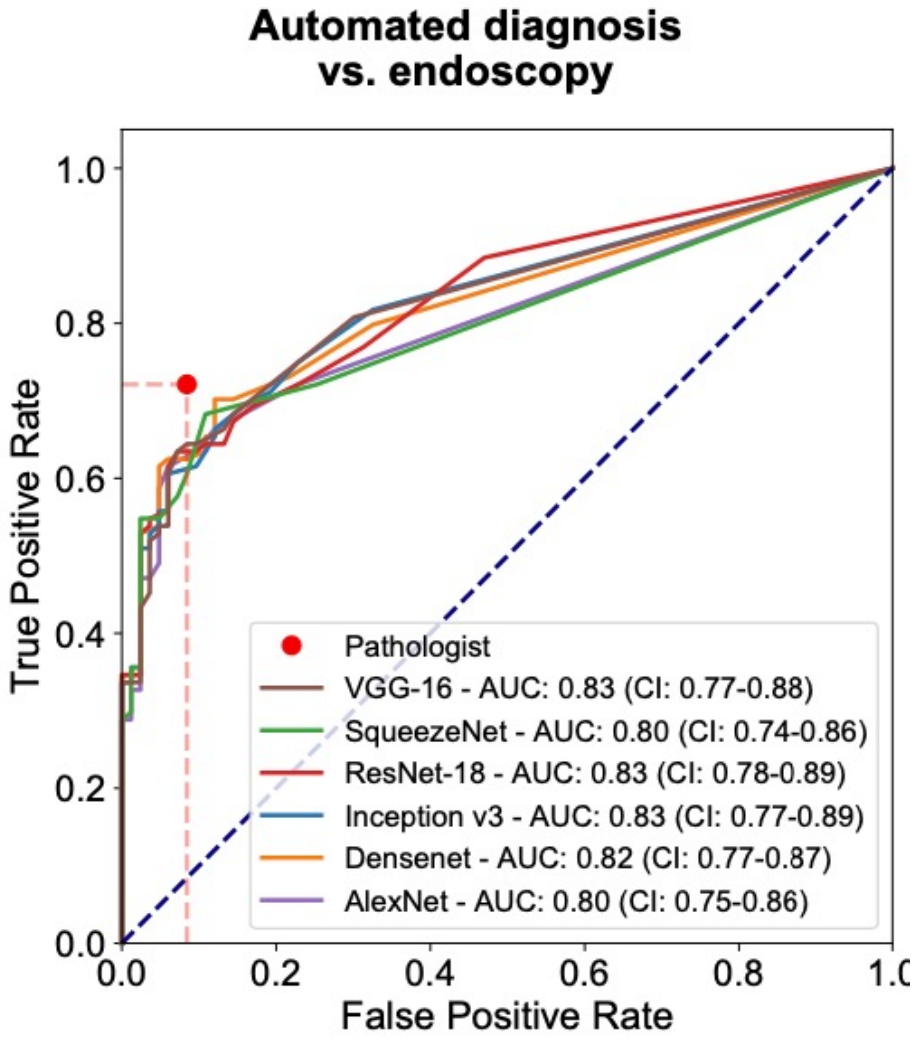
Cytosponge procedure



Deep learning models

Benchmarking of different approaches



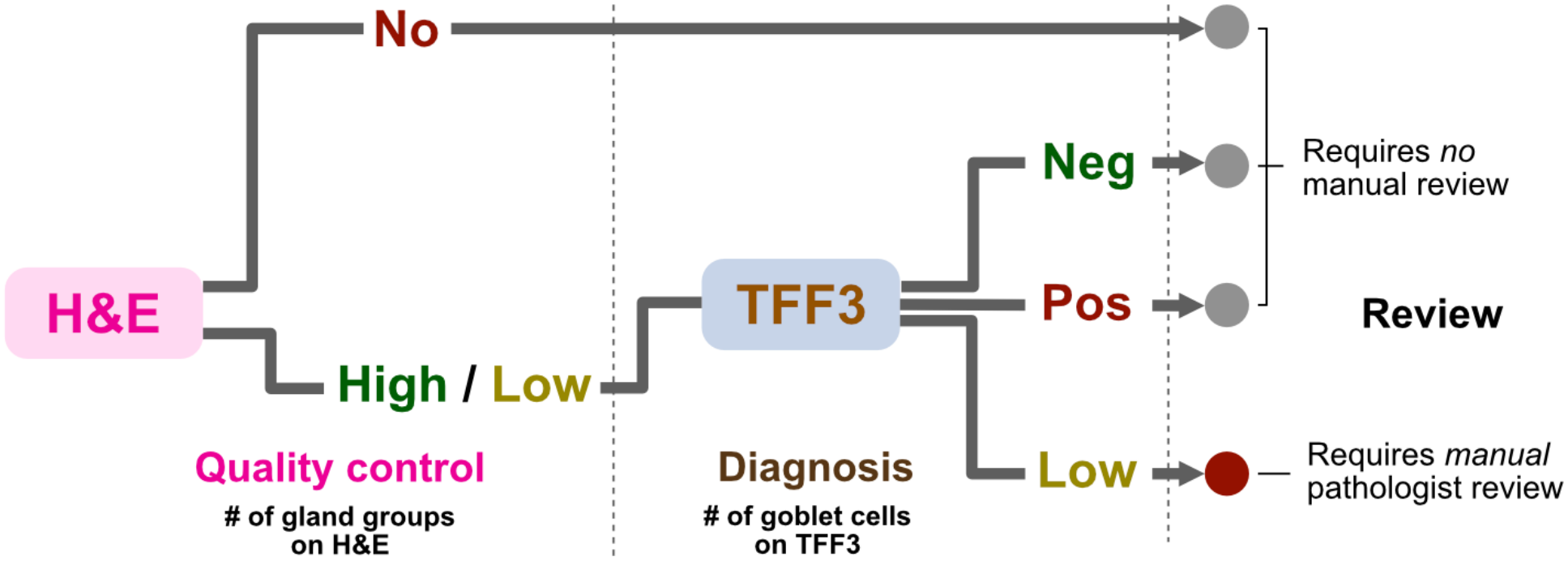


Triage-driven diagnosis

- Stratify patient samples into confidence-based groups:

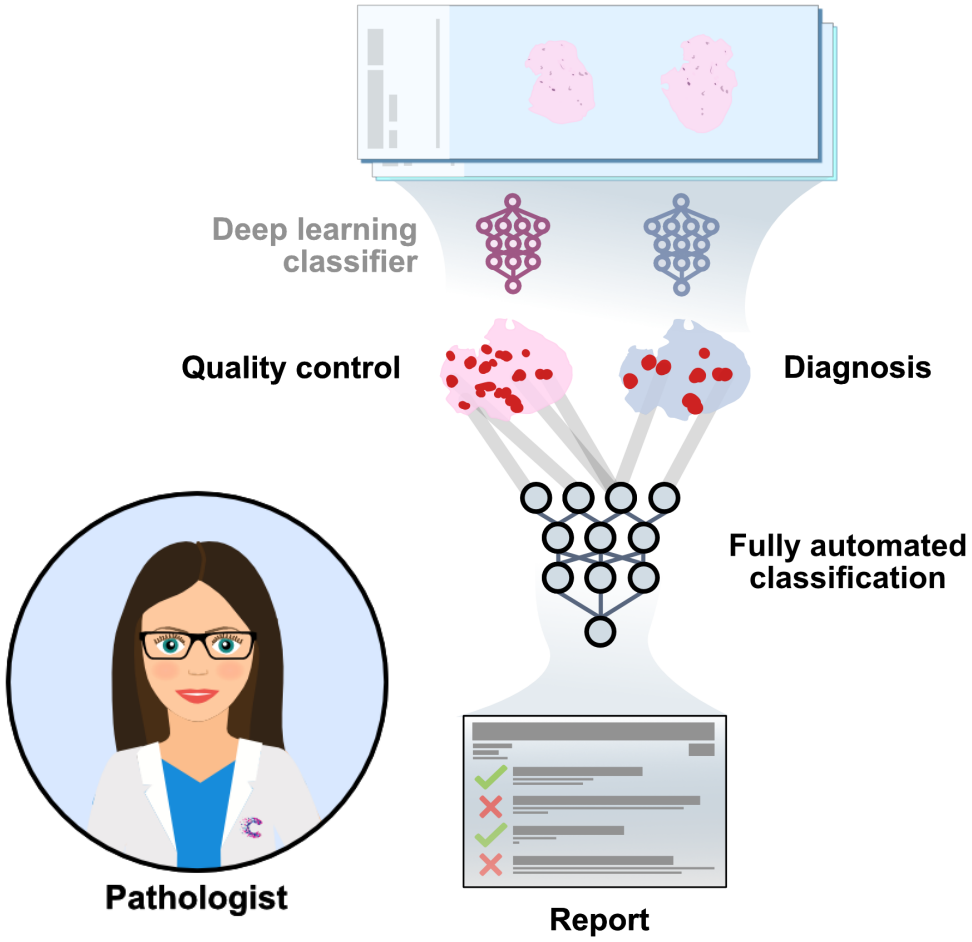
Easy cases:
automated review

Difficult cases:
manual review

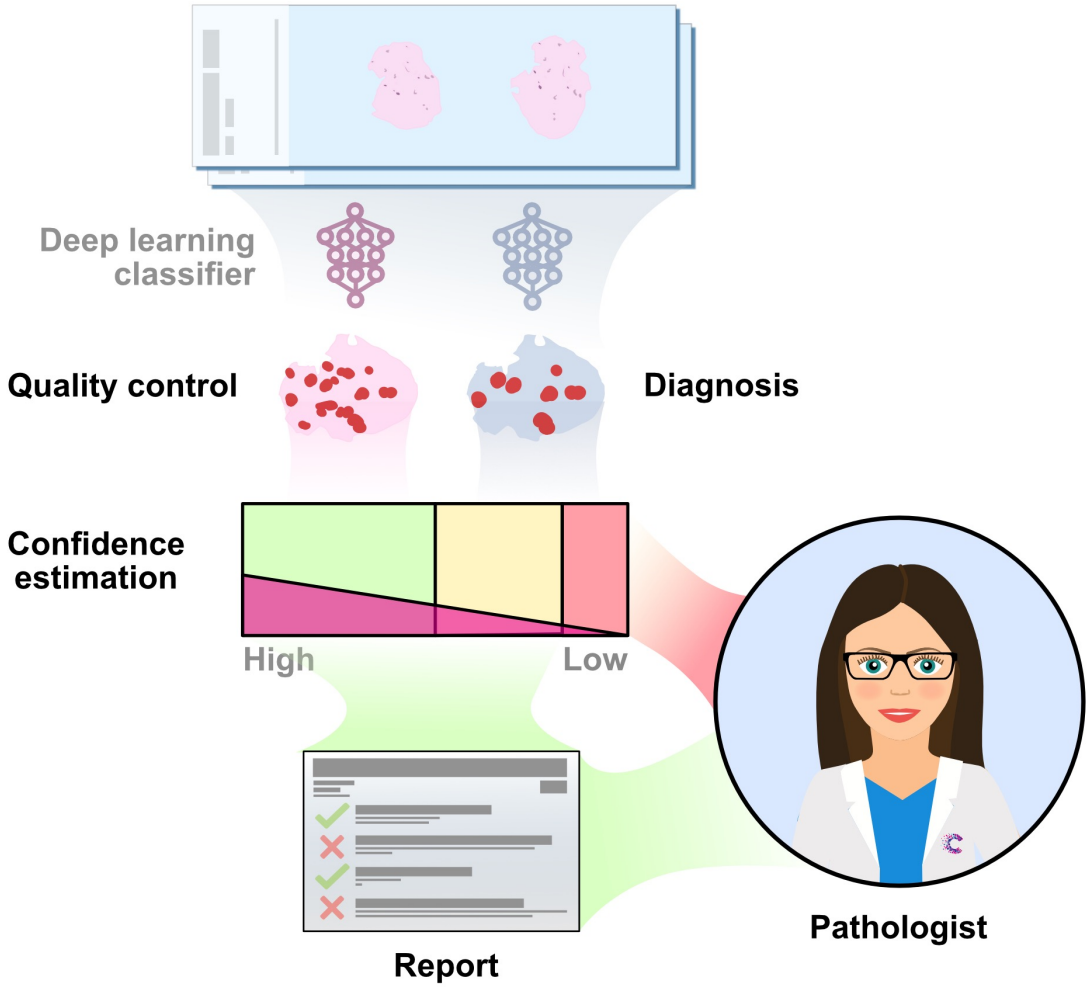


Automation approaches

Full automation

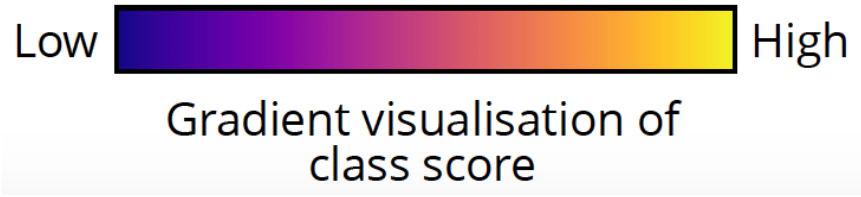


Semi-automation



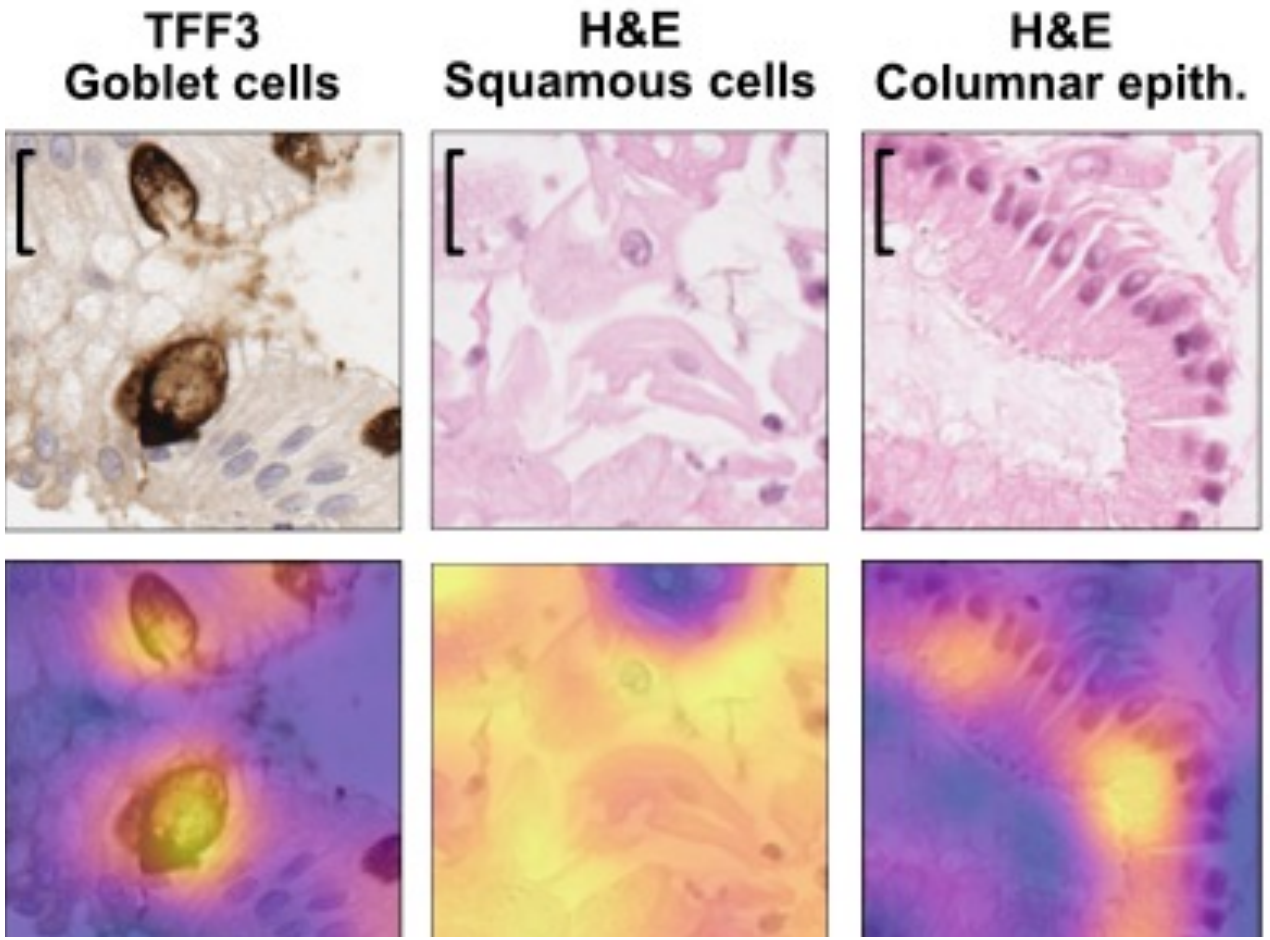
Black boxes?

Interpretation of individual tile decisions



Tile image

Saliency map (Grad-CAM)



What is the extent, diversity and origin of chromosomal instability pan-cancer?

Dr. Ruben Drews

A pan-cancer compendium of chromosomal instability
R. Drews et al

To appear June 15th, 2022

github.com/markowetzlab/Drews2022_CIN_Compendium

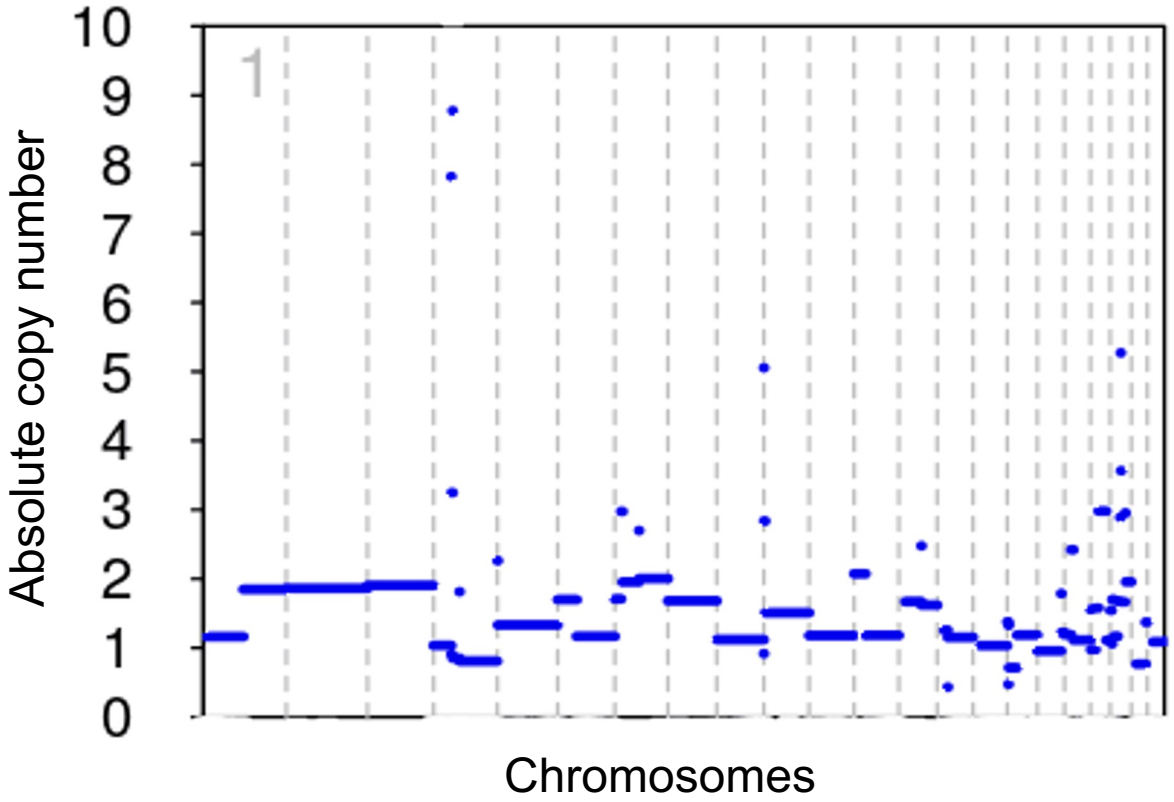
Dr Geoff Macintyre

Dr Peter Van Loo

Prof James Brenton

Chromosomal instability (CIN)

Example:
117 high-grade serous ovarian cancers



- Genomic chaos
- Pervasive TP53 mutations
- Few recurrent changes
- no clinical stratifier beyond germline BRCA1/2

CIN-low **CIN-high**

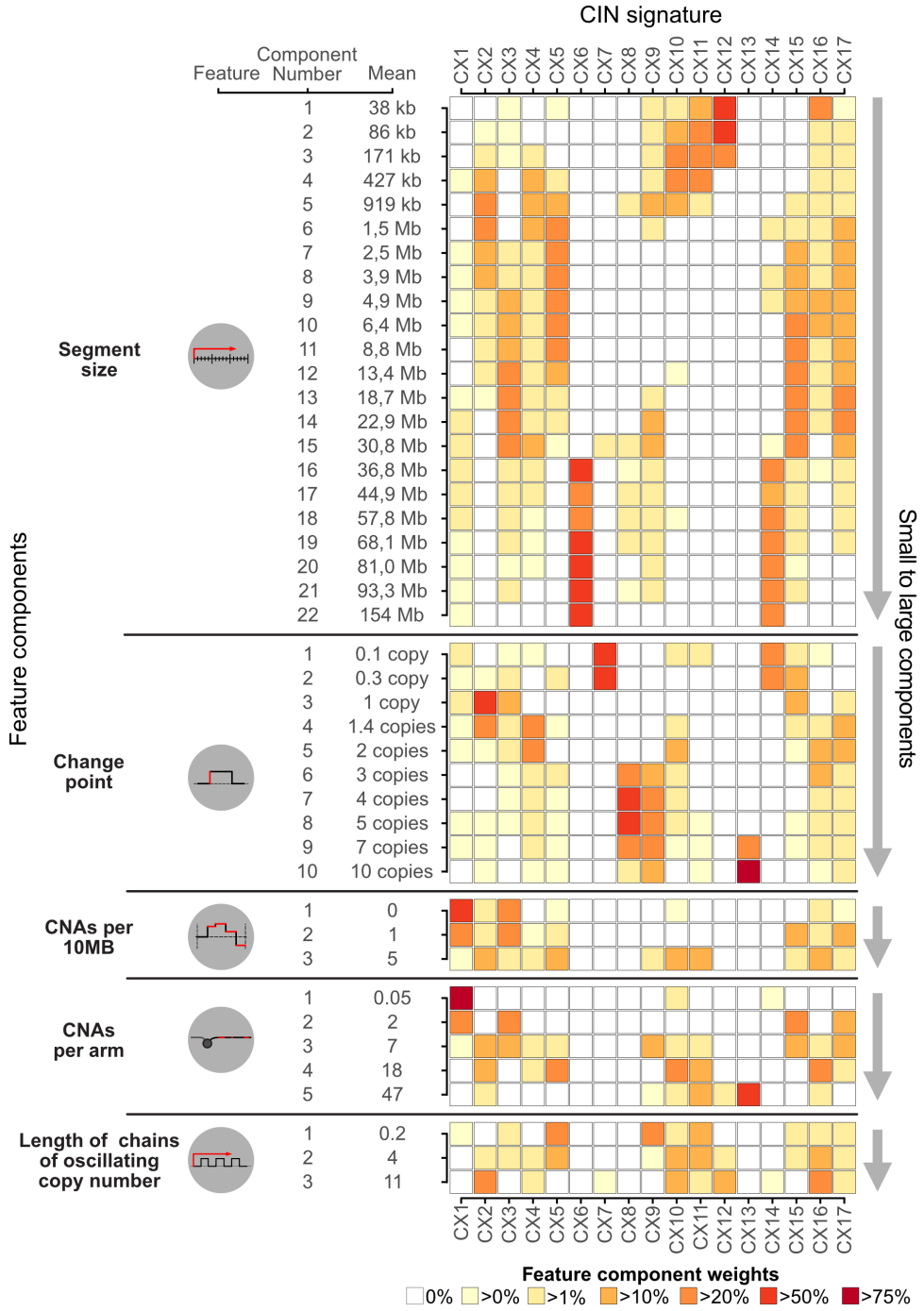
-1-
Quantitative measures

-2-
Different types

-3-
Dynamics + heterogeneity

17 copy number signatures

Each signature is a characteristic genomic pattern = set of features



Drews et al 2022

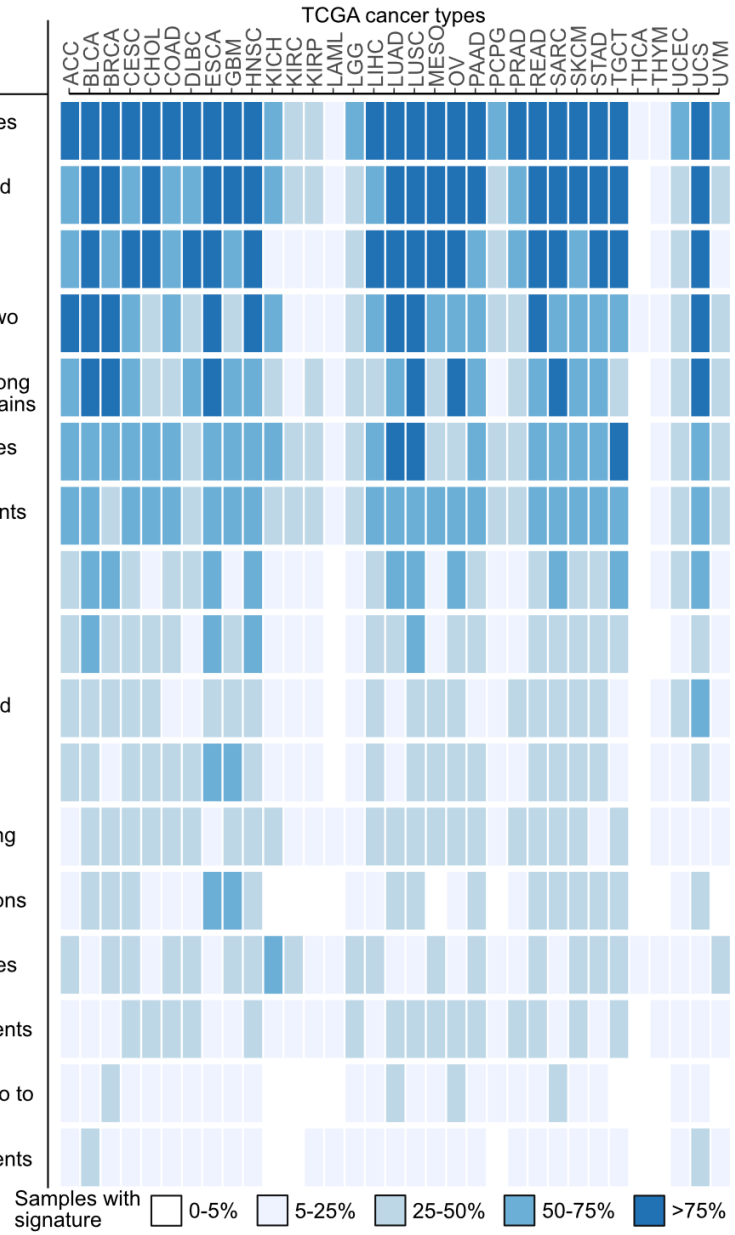
Link signatures to putative causes

c) Example three star rating for CX3

Mutated genes	BRCA1, BRCA2	Impaired homologous recombination
+ ★★	PIK3R2, MYC1 PPP2R1A, MAPK1	Replication stress
	TP53	Impaired DNA damage sensing
	ERCC2	Impaired nucleotide excision repair (NER)
Pattern of change	Segment size is indicative of large-scale state transitions, a genomic hallmark of HRD (Popova et al., 2012).	
	One copy change hints to both loss-of-heterozygosity events and tandem duplications.	
Orthogonal data	Tandem duplication classes 1, 1/2, 2	Hallmarks of homologous recombination deficiency (HRD)
+ ★	SV signatures 1, 3, 5	
	SBS signature 3	
	ID signature 6	
	Ovarian CNA signatures 3, 7	
	Loss-of-heterozygosity	
	Seven other HRD metrics	
	Improvement in PFI and OS for ovarian cancer patients	Platinum-sensitivity

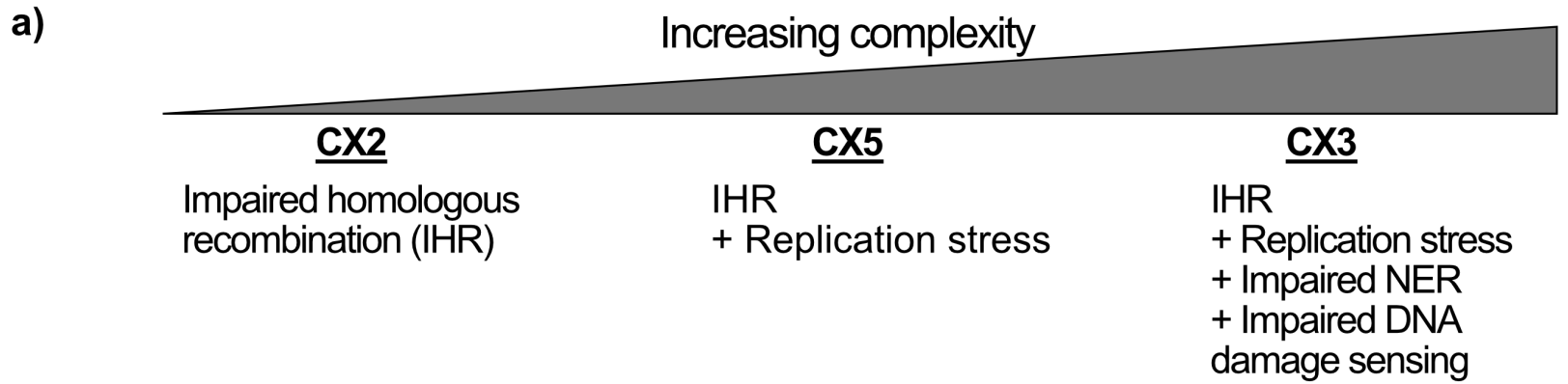
Drews et al 2022

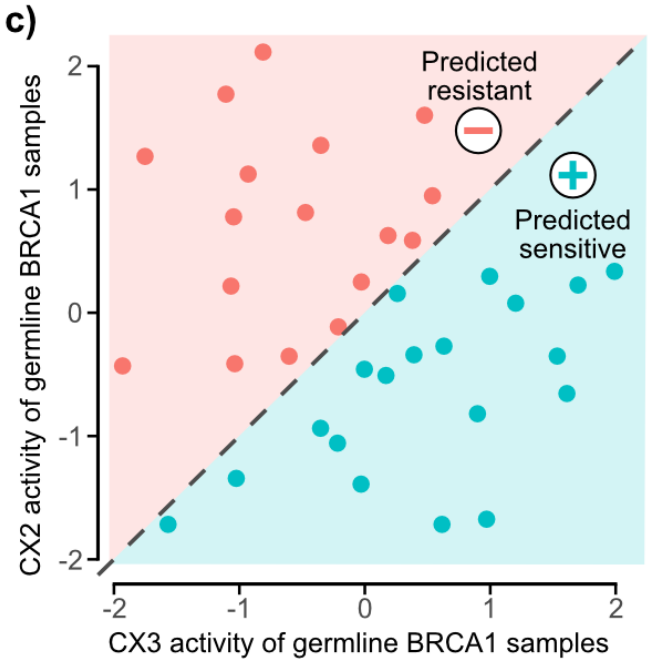
Signature	Pan-cancer prevalence	Putative cause	Confidence	Pattern of change
CX1	80%	Chromosome missegregation via defective mitosis and/or telomere dysfunction	★★★	Whole arm/chromosome changes
CX2	69%	Impaired homologous recombination (HR)	★★★	Clustered, short to medium-sized segments
CX3	63%	Impaired HR with replication stress and impaired damage sensing	★★★	Long segments with one copy change
CX4	58%	PI3K/AKT-mediated toleration of whole-genome duplication	★★★	Short and long segments with two copies change
CX5	56%	Impaired HR with replication stress	★★★	Clustered, medium to medium-long sized segments in oscillating chains
CX6	51%	Chromosome missegregation via SCF-complex dysregulation	★★★	Whole arm/chromosome changes
CX7	50%	Unknown	☆☆☆	Segments with small changepoints
CX8	38%	Replication stress	★★★	Low-level amplifications
CX9	32%	Replication stress	★☆☆	Mid-level focal amplifications
CX10	29%	Impaired NHEJ with replication stress	★★☆	Clustered, short to medium-sized segments
CX11	28%	Loss of cell-cycle control with replication stress	★★★	Clustered, short segments
CX12	27%	Unknown	☆☆☆	Short segments in long oscillating chains
CX13	26%	Replication stress	★☆☆	High-level, clustered amplifications
CX14	26%	Chromosome missegregation via defective mitosis	★★☆	Whole arm/chromosome changes
CX15	25%	Unknown	☆☆☆	Clustered, medium-sized segments
CX16	17%	Impaired DNA repair	★☆☆	Clustered, short segments of two to three copies
CX17	16%	Replication stress	★★☆	Clustered, medium-sized segments of one to two copies

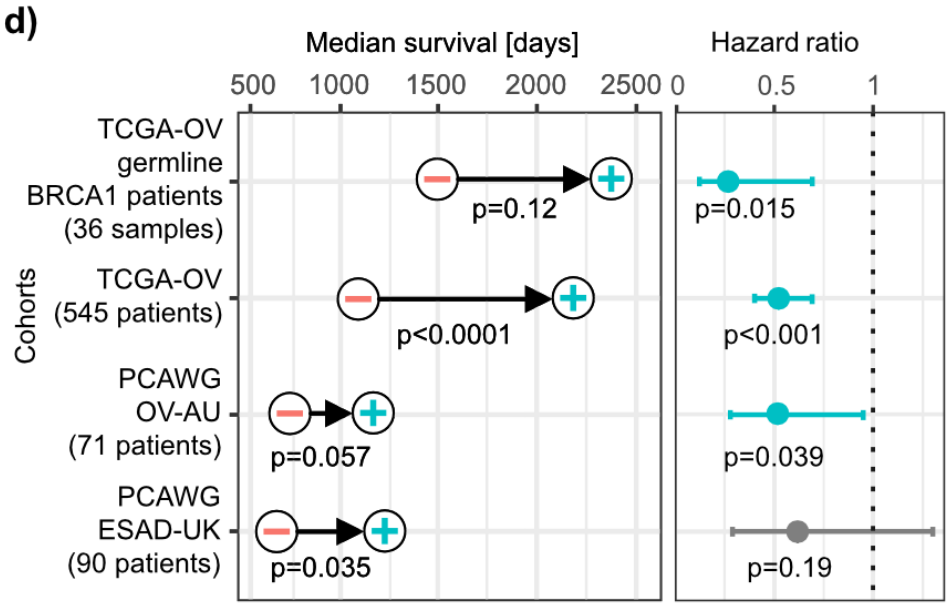


Drews et al 2022

Case study: Predicting platinum-sensitivity





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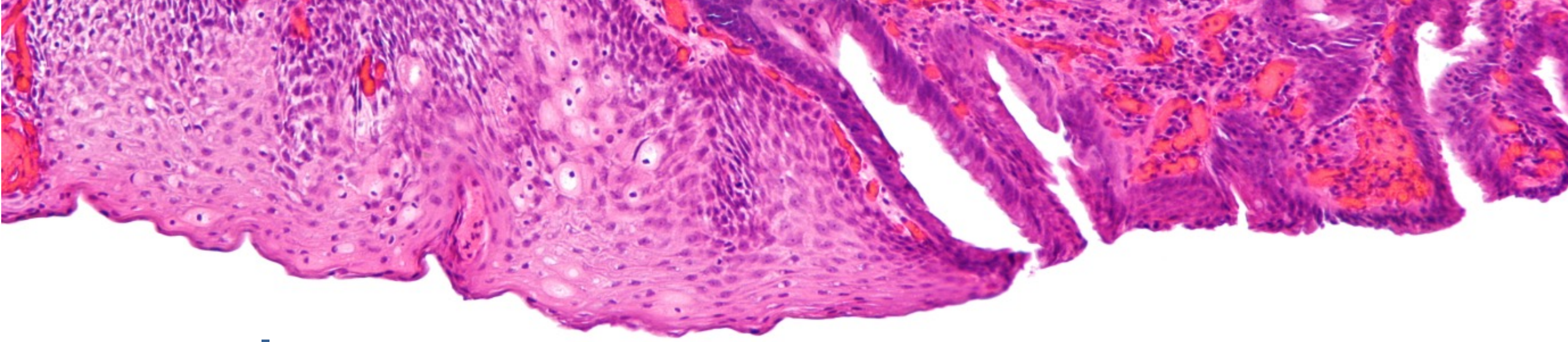
CAUSALITY
nature
Systems Genetics
Large-Scale Inference
Machine Learning
PATTERN RECOGNITION AND MACHINE LEARNING
CHRISTOPHER M. BISHOP



Finding patterns in images and genomes with AI

Florian Markowetz

www.markowetzlab.org

@markowetzlab