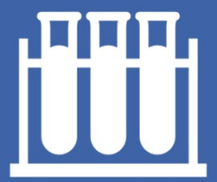
BEHIND THE SCIENCE

AMY SOBEL
FOUNDATION



Introduction

The Amy Sobel Foundation hopes to save lives by promoting awareness and supporting innovative research to prevent IBD-related cancer. This document provides more detail about the science behind our work by answering three questions:

1. **What is the relationship between IBD and cancer?**
2. **Why is detecting cancer so difficult in IBD?**
3. **How can we do better with a new approach?**

IBD & CANCER

1

IBD Basics

DNA and Accelerated Aging

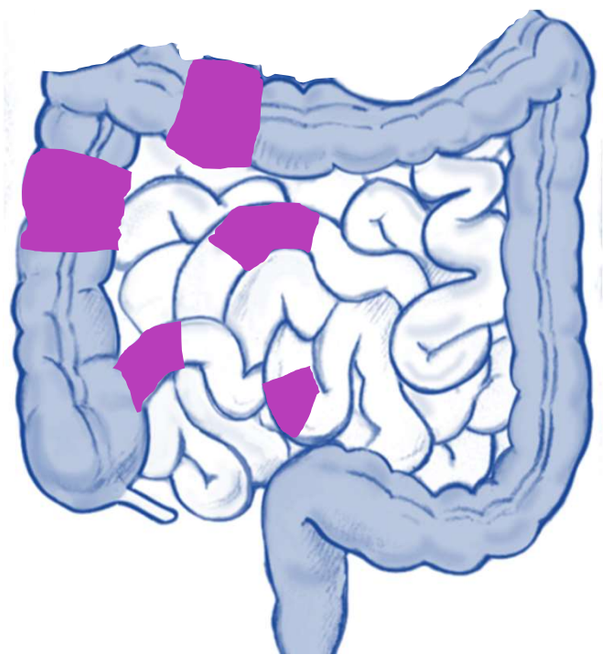
Cancer Risk and Outcomes

In inflammatory bowel disease, the immune system becomes dysregulated, causing inflammation and tissue damage. The main types of IBD are Crohn's and ulcerative colitis.

IBD basics

Crohn's Disease

Crohn's disease can occur in any location from the mouth to the anus. Diseased tissue is often interspersed with normal tissue.[1]



Ulcerative Colitis

Ulcerative colitis affects the colon and extends continuously. For some patients it is limited to the rectum; for others it extends up the left side or across the entire colon.[2]

Fast Facts

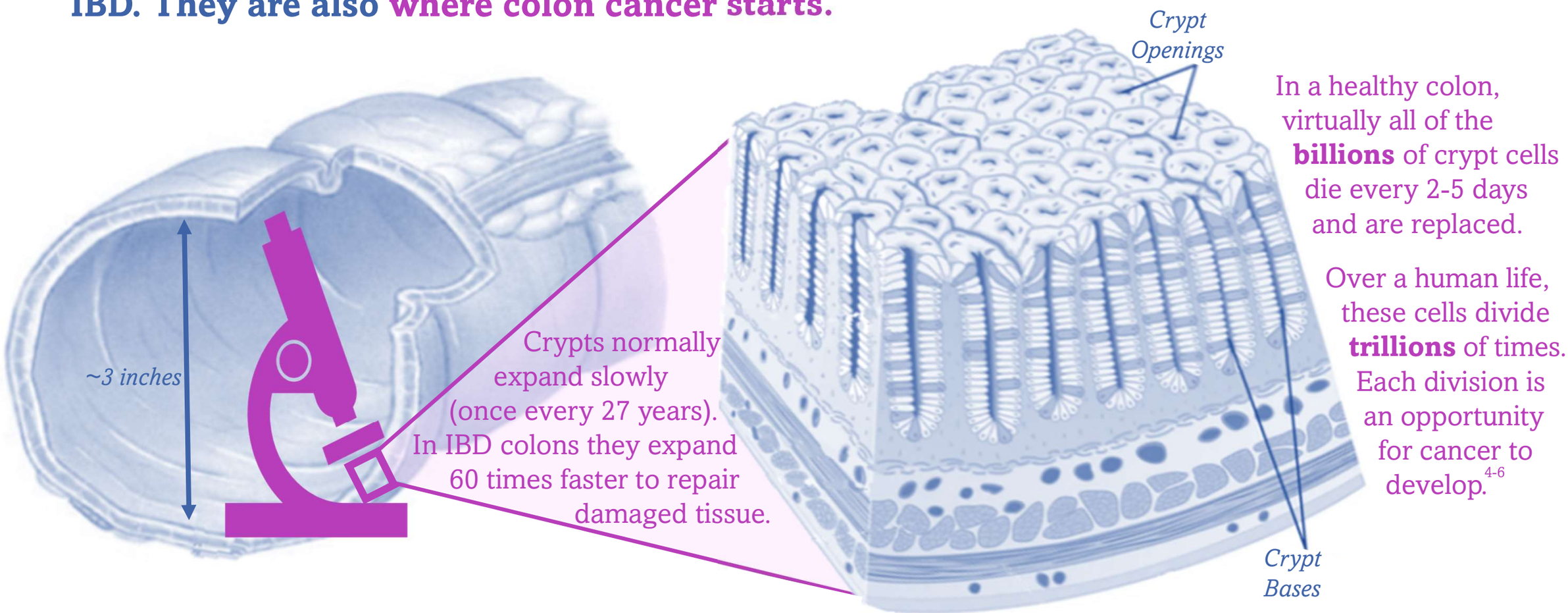
>7 million patients worldwide
1.6 million U.S. patients
Global incidence is on the rise[3]

Living with IBD

Stomach Pain	Fever
Bleeding	Chills
Diarrhea	Obstruction
Urgency	Perforation
Fatigue	Infertility
Anemia	Cancer

Tales from the crypt

The colon is lined by millions of U-shaped glands, called crypts. Crypt cells secrete mucus and absorb water. They are the cells under attack by the immune system in IBD. They are also where colon cancer starts.

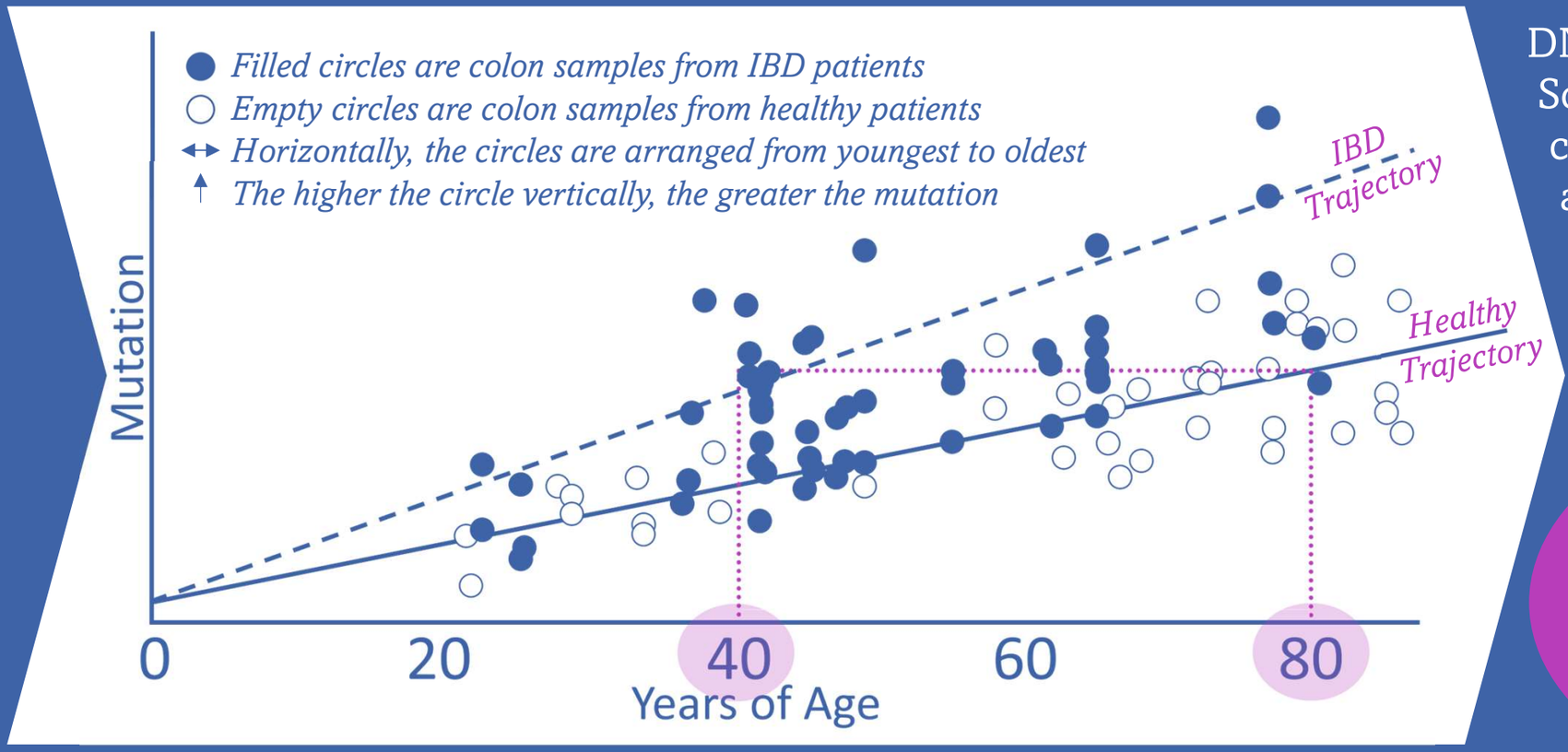


In a healthy colon, virtually all of the **billions** of crypt cells die every 2-5 days and are replaced.

Over a human life, these cells divide **trillions** of times. Each division is an opportunity for cancer to develop.[4-6]

Accelerated aging

IBD increases cancer risk by accelerating the aging of the colon. This acceleration is directly related to inflammation: how long, how extensive, and how severe.[7-10]



DNA damage is called **mutation**. Some mutations originate at conception, but many more accumulate naturally as we age. This is why older people have more cancer. In IBD, mutation accelerates in the colon.

By the age of 40, a person with colitis may have a colon that is "biologically" older than a person without colitis at age 80[11,12]

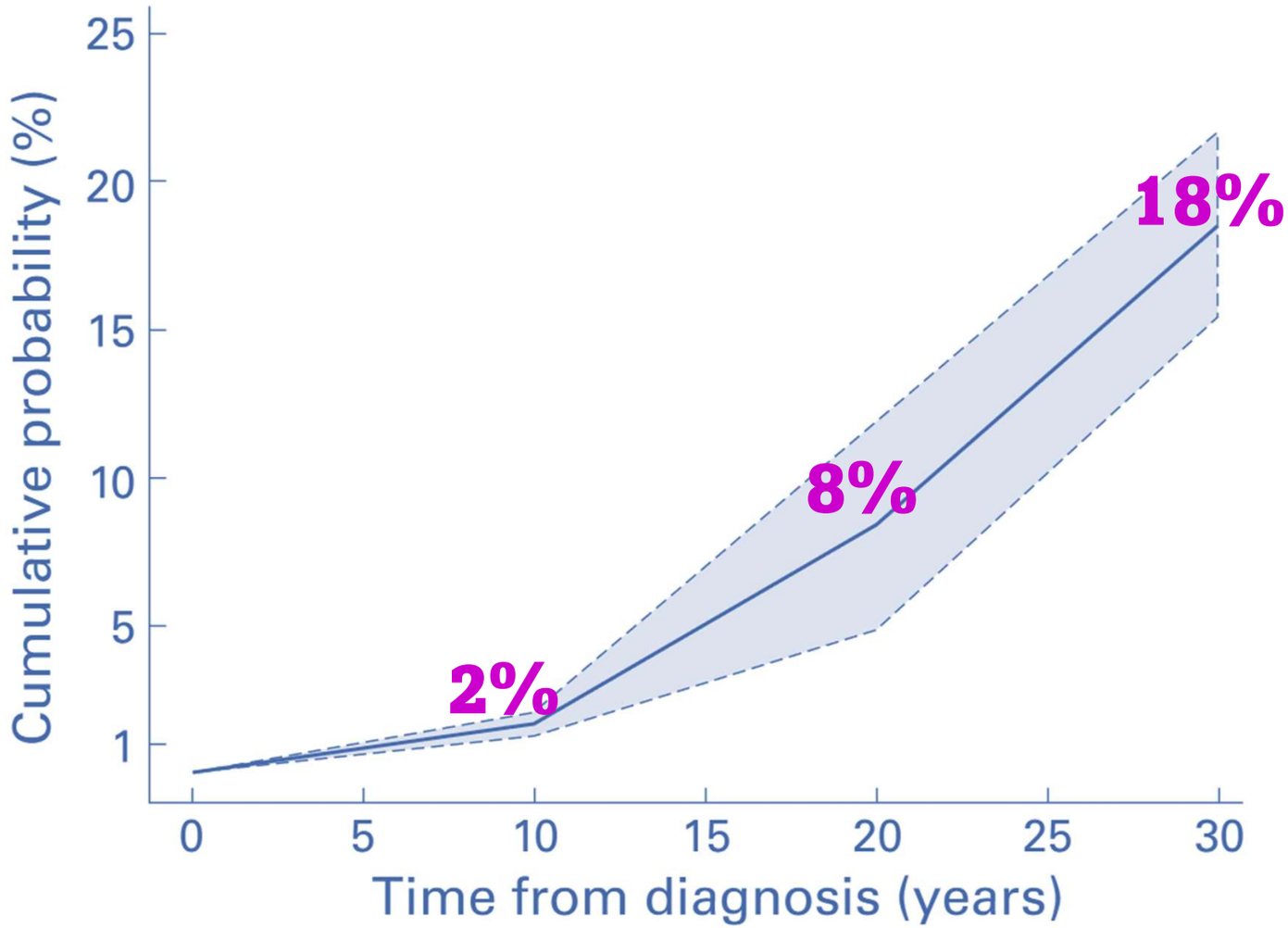
Cancer risk in IBD

IBD patients have **2- to 4-times greater risk** of cancer than healthy people[13-17]

1 in 8 IBD patients eventually develop colon cancer[14-20]

The **cancer risk grows over time** and **varies widely** across patients based on **multiple factors**[20, 21]

We have known about cancer risk in IBD for 100 years and began special screening programs 50 years ago[22-24]



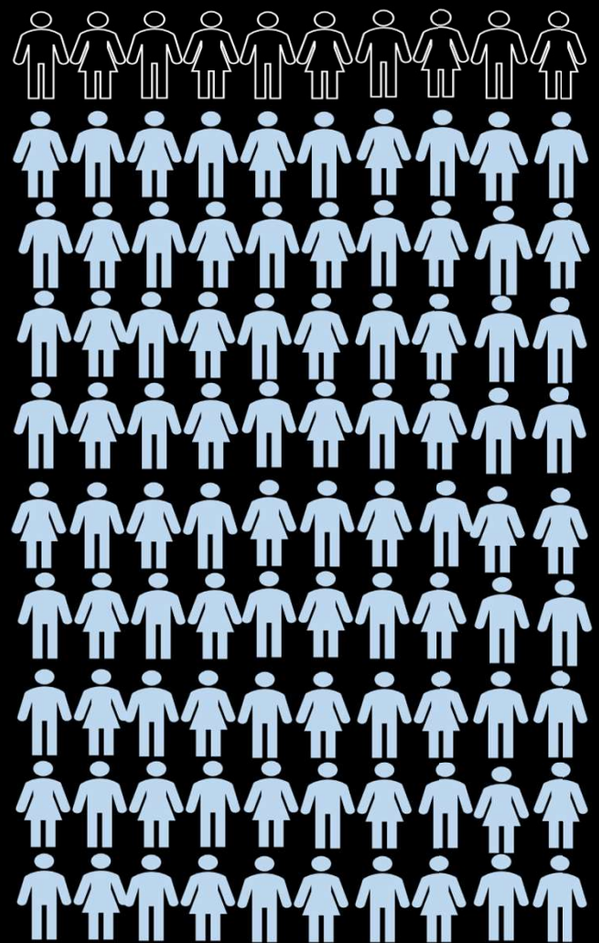
Colon cancer survival

Early detection is critical for survival in colon cancer

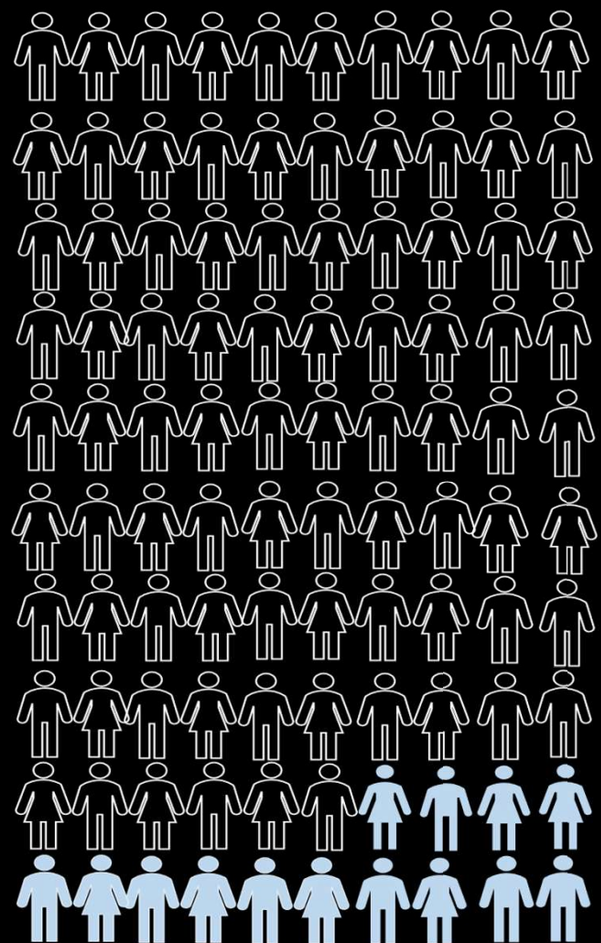
90%
Early Survival

14%
Late Survival[25]

Early Detection



Late Detection



CANCER DETECTION

2

Surveillance Tools

Importance of Early Detection

Distinct Features of IBD-Related Cancer

Challenges of Current Surveillance

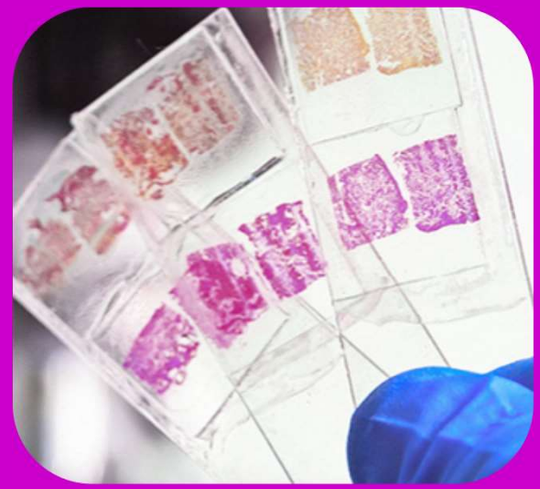
Cancer surveillance

Colon cancer surveillance consists of a search for abnormalities during a colonoscopy and subsequent pathology review of biopsy samples.[26, 27]

An **endoscope** transmits video to visually detect polyps or dysplasia

A claw on the endoscope snips **biopsies** (bits of tissue)

The biopsies are sliced very thin for review by a **pathologist** under a **microscope**



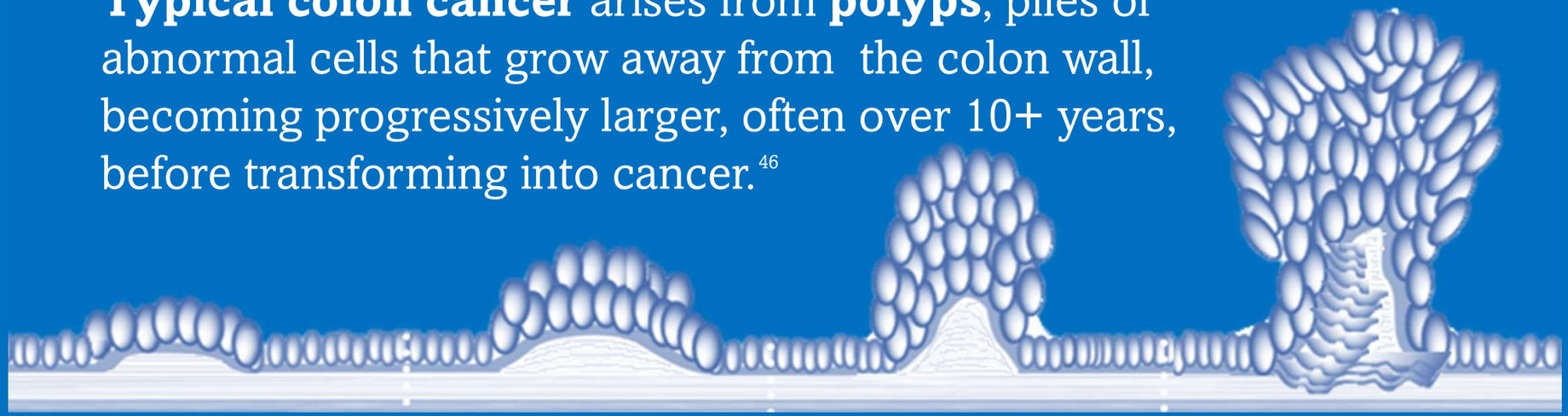
Colonoscopic surveillance and management has resulted in important improvements in patient safety in IBD.[28-33]

But surveillance for IBD patients is different than screening for average risk patients – and less effective.[34-41]

Up to 50% of IBD-related cancer is missed during cancer surveillance

IBD cancer is different[17, 42-45]

Typical colon cancer arises from **polyps**, piles of abnormal cells that grow away from the colon wall, becoming progressively larger, often over 10+ years, before transforming into cancer.[46]

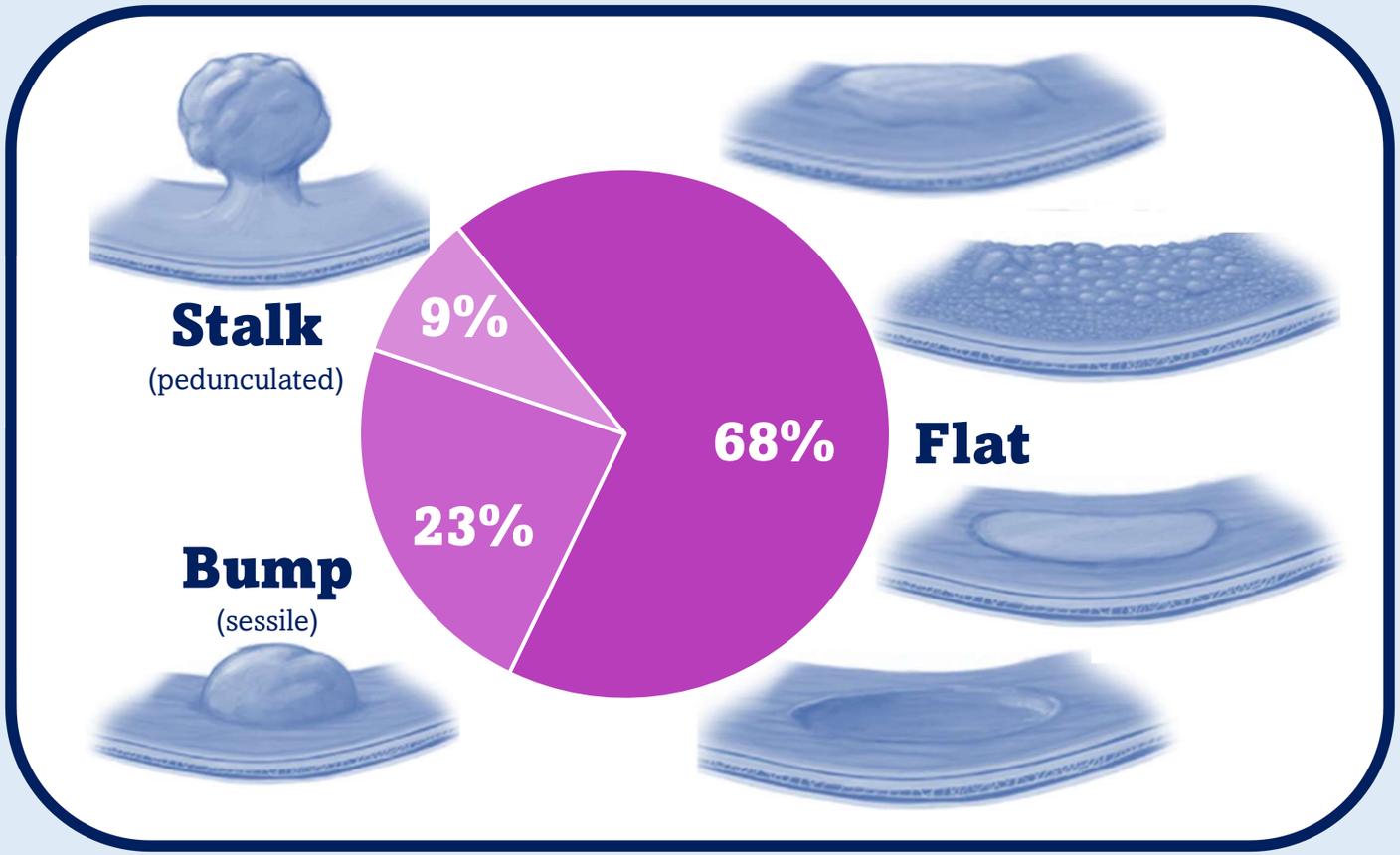


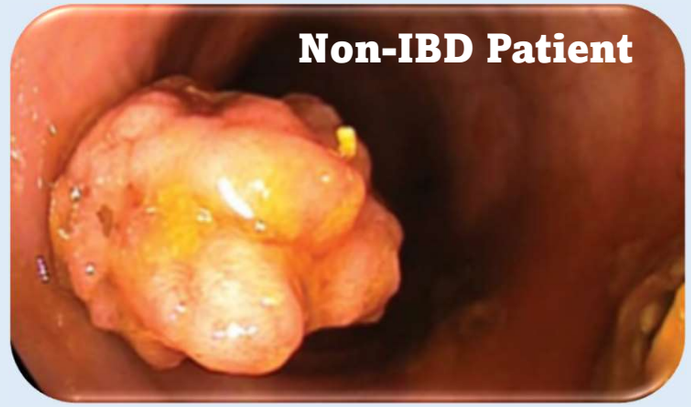
IBD-related cancer begins with a kind of tissue damage called **dysplasia** that spreads along the colon wall or invades down rather than popping up. It also develops into cancer faster, in 1-3 years.[32, 47-49]

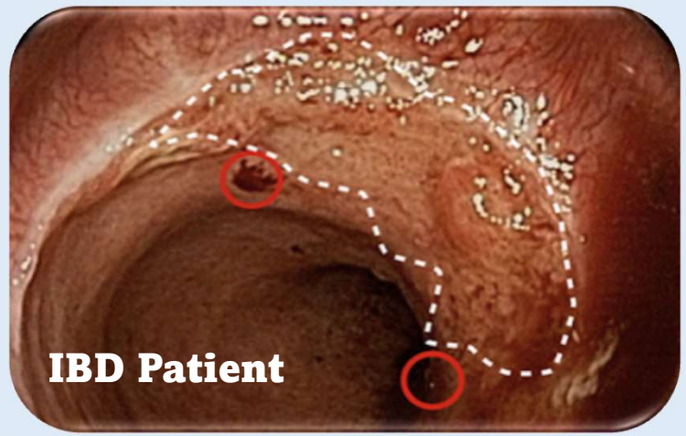
- Younger Patients
- More Difficult to Detect
- More Aggressive
- More Resistant to Treatment

70% of IBD dysplasia is flat

Though most dysplasia does not develop into cancer, flat dysplasia is much more likely to progress.[32, 50-52]







A biopsy covers **1/20th of 1%** of the colon – not very much![53]

The IBD cancer above was **missed**; biopsies (red) were taken outside the margins of the growth (white). This **sampling error** meant a delayed diagnosis for the patient.

Grades of dysplasia

Pathologists classify dysplasia into categories, called grades, to indicate the degree of abnormality.[54, 55]

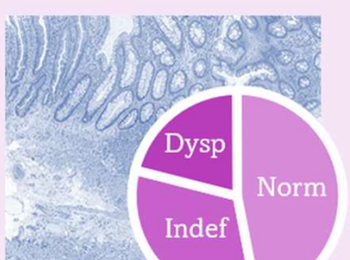
A problem in IBD cancer surveillance is that **active inflammation** can render biopsies **unreadable**. In other words, the patients at **highest risk**, those with persistently active disease, are **more likely** to have pre-cancer that is **difficult to identify**.[56-58]

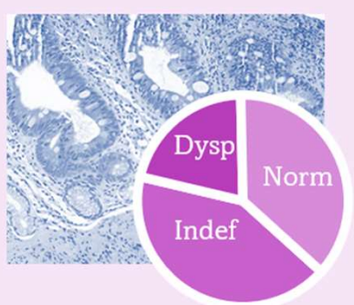
Dysplasia? Maybe?

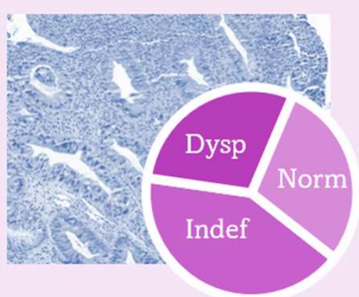
Grading dysplasia is subjective and experts can disagree.[58-60]

The dysplasia samples below were reviewed independently by 20 expert pathologists. The pie charts highlight the **interobserver variability**.[61]

Failure to correctly identify dysplasia can be an important issue. Even a single finding of "indefinite" dysplasia significantly changes a patient's risk.[31, 62-64]



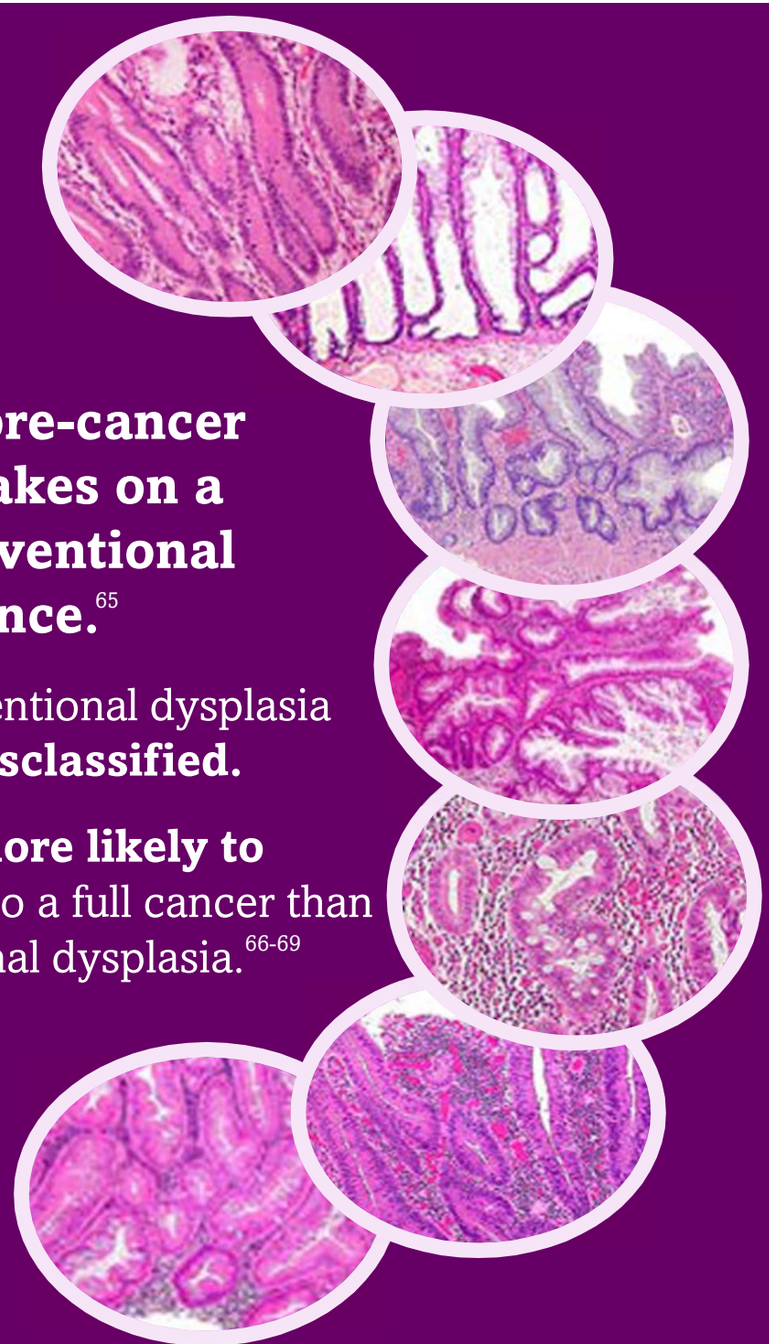




40% of pre-cancer in IBD takes on a non-conventional appearance.[65]

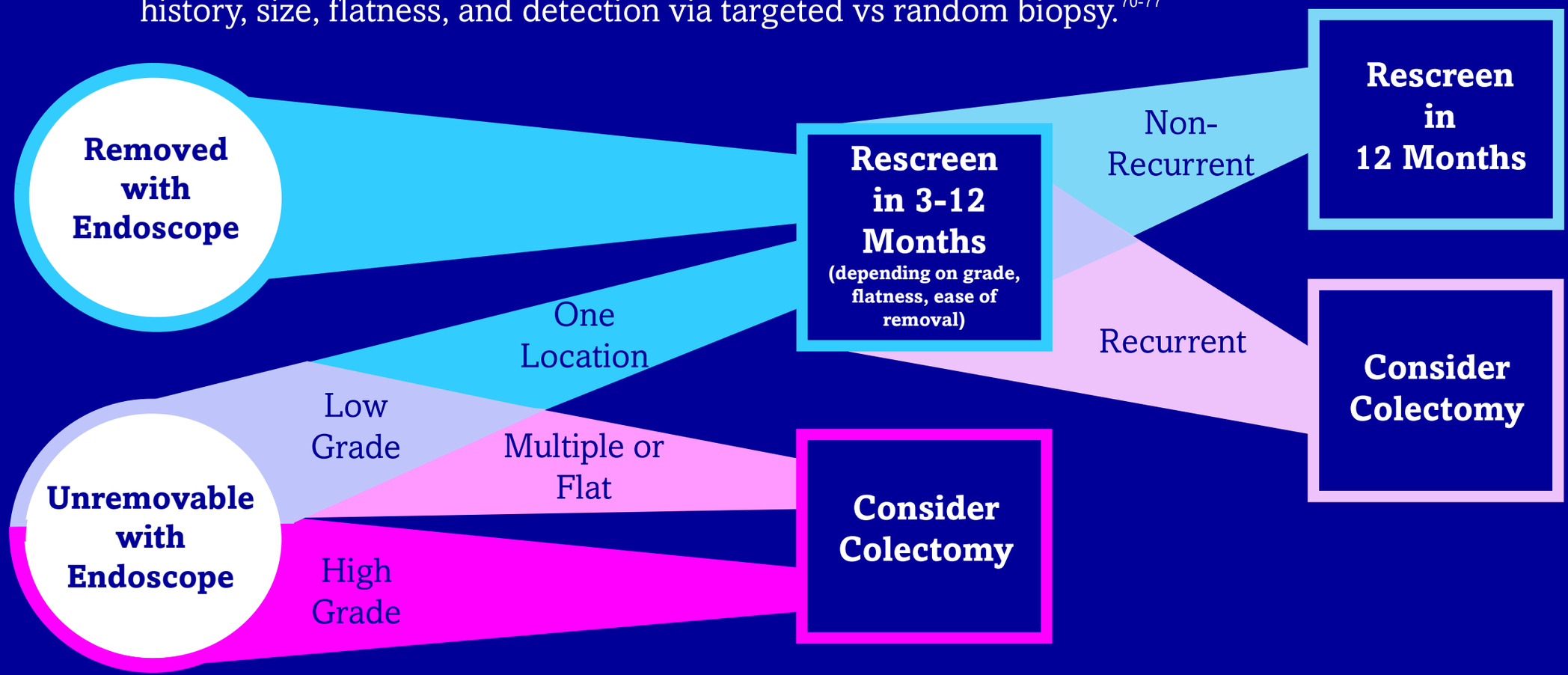
Non-conventional dysplasia is often **misclassified.**

It is also **more likely to progress** to a full cancer than conventional dysplasia.[66-69]



Managing dysplasia

There is no universally agreed upon framework for managing dysplasia. Strategies rely on factors such as resectability, grade, extent/location, prior history, size, flatness, and detection via targeted vs random biopsy.[70-77]



Colectomy

The decision to undergo colectomy is often difficult. Surgical removal of the colon is a major procedure with major possible complications. It also means a temporary ostomy bag if not a permanent one.

In surveys of IBD patients about what level of cancer risk they think warrants a colectomy, responses cluster around **50%**.

Patients are willing to take a coin toss on colon cancer to avoid this surgery.

In the absence of individualized risk information, patients are left to choose between a **colectomy they very likely don't need** and "some" risk of a **cancer they could otherwise avoid**.[78-81]

Colectomy Complications

Bleeding
Thrombosis
Embolism
Infection
Impotence
Infertility
Bladder damage
Nerve damage

Which patients get cancer?

We don’t know.
But most do not.
And our system is tailored toward the average.

As a result:

We spend **too much** time, energy, and money on heightened surveillance of patients at no greater risk than the general public.

We do **too little** escalated monitoring and communicating with patients who are at very high cancer risk.[82-85]

OUR NEW APPROACH

3

Molecular Testing

Patient Impact

Our All-Star Team

The Study and Next Step

Molecular testing

Today, a technological revolution is underway.

Using cutting edge technology, we can identify cancer-related DNA changes in real time at molecular resolution.

Next Generation Sequencing (NGS) will be a powerful new tool to add to our cancer surveillance arsenal in IBD.[86]

Molecular testing can be smoothly integrated into existing IBD workflows

Pathologists routinely extract **DNA** from other biopsy types and send it out for sequencing

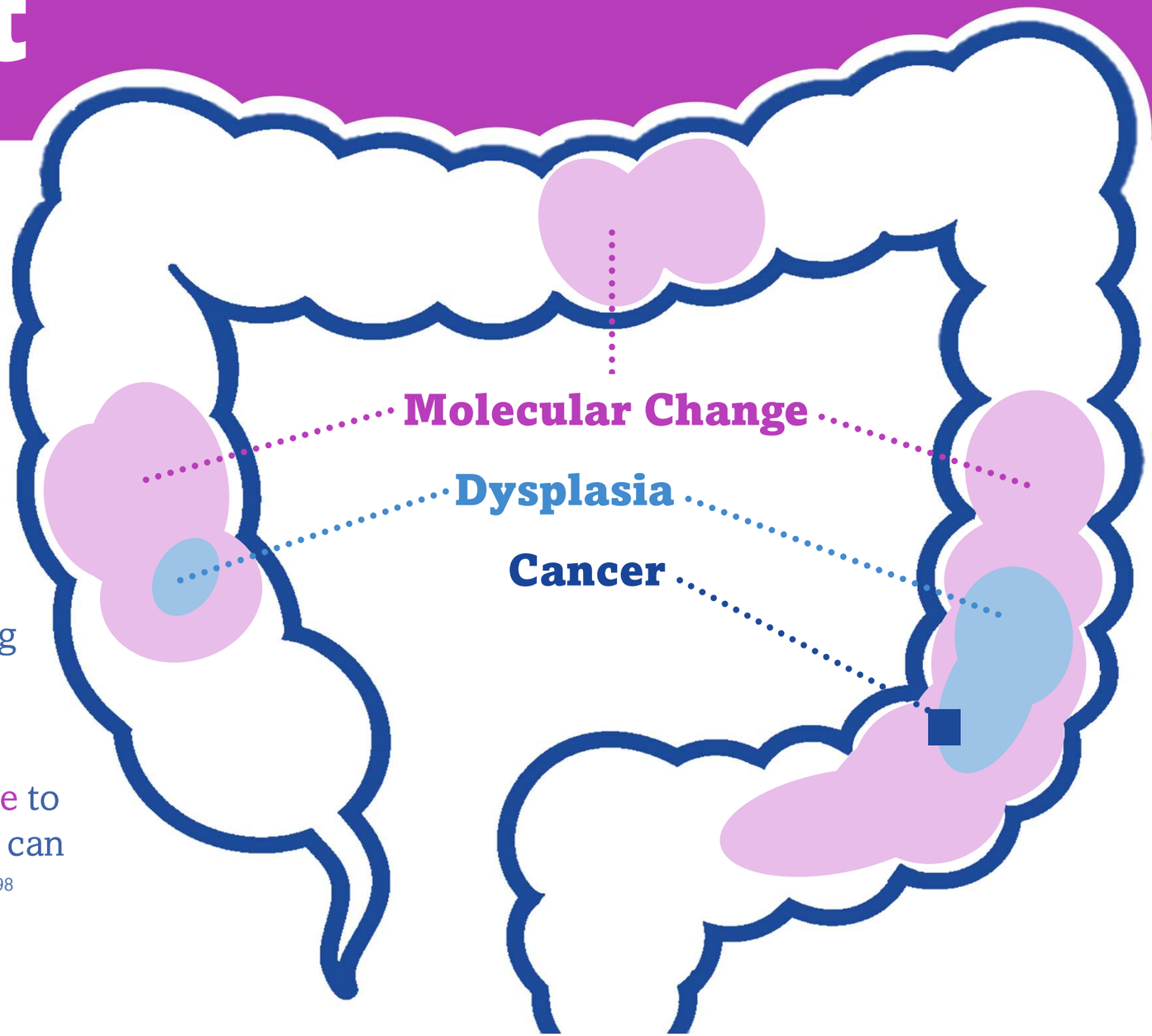
Costs are rapidly **decreasing** and clinical **usage** is **growing**

Field effect

Cancer-related molecular changes in IBD are typically widespread, a phenomenon called the field effect or field cancerization.

The size of pre-cancerous fields helps us improve early detection by reducing sampling error. We don't need to find the exact cancer cells. We can rely on detecting broader fields of cancer-primed cells.[87-97]

The field effect also opens the window for early detection. Molecular changes invisible to the naked eye or even under a microscope can be detected up to 8 years ahead of cancer.[98]



Patient benefit

To be useful, a test must improve patient outcomes. There is a clear, unmet clinical need in IBD.

We believe a molecular test to predict cancer will save the lives of IBD patients.

Heightened Surveillance for High-Risk Patients

Some patients develop cancer after one finding of indefinite dysplasia. Others never progress despite multiple findings of low grade dysplasia. Differences not visible to the naked eye or the microscope are visible at the molecular level, allowing us to increase surveillance for those with the highest risk.

Early Surveillance for Patients at Risk of Early Cancer

Current guidelines call for cancer surveillance to begin 8-10 years after IBD diagnosis, but 17-28% of IBD cancer cases occur earlier. Molecular testing at the time of IBD diagnosis would allow for higher risk patients to begin surveillance earlier.[17, 99]

Reduced Surveillance for Low-Risk Patients

IBD patients often suffer from anxiety and depression. Cancer risk and regular cancer surveillance is an unnecessary added stressor for many patients. A test that can predict freedom from cancer with very high accuracy might allow for changes to surveillance schedules or at least provide peace of mind.

Better Informed Colectomy Decisions

Some patients undergo colectomy for IBD symptom relief, but many do not require it. Colectomy for cancer prevention is sensible only in extremely high-risk patients. A highly predictive test for future cancer would be an important new tool to aid decision-making.

All-Stars

To develop a test, we're working with **Kit Curtius** and **Trevor Graham,** two of the world's leading experts on cancer evolution and on IBD-related cancer.[9, 32, 88-93, 99-103]

We are building on their groundbreaking work to trace the **evolution of molecular changes** that occur to cellular DNA as IBD patients progress towards cancer.

Pilot project

Kit and Trevor's most recent work is a case-control study of progression of IBD to high grade dysplasia or cancer.

Dysplasia is the starting point because we expect the molecular signature to be strongest. These are also the patients who face the most difficult clinical decisions.[104]

20-30% of IBD patients with low grade dysplasia will progress...
But we don't know which ones [103-106]

The project began with a discovery cohort of 67 patients at St. Mark's Hospital in London, one of the world's leading IBD specialist hospitals, to develop a cancer-prediction algorithm. They subsequently tested the algorithm in an independent validation cohort of 51 patients from three other UK hospitals.

Discovery Cohort

22 progressors
45 non-progressors

St MARK'S HOSPITAL

Validation Cohort

17 progressors
34 non-progressors

UNIVERSITY OF OXFORD

Newcastle University

QUEEN'S UNIVERSITY BELFAST

Progressor samples were IND or LGD biopsies from 1-5 years prior to subsequent detection of HGD or cancer. The median antecedent biopsy was taken 427 days prior to progression.

Non-progressor samples were IND or LGD biopsies from at least five years ago without subsequent HGD or cancer detected during follow up.

Strong results

Kit and Trevor's test was as accurate as a mammogram and superior to existing stool- and blood-based colon cancer tests.

It predicted 82% of all future cancers and was correct 89% of the time when predicting progression.

Patients designated **high risk** had a **93% chance of progressing** in the next four years.

Patients designated **low risk** had a **96% chance of not progressing** in the next four years.

	Detection Rate	*False Positive*
IBD Cancer Test Progression from Dysplasia	**82%**	**11%**
Mammogram[107] Breast Cancer	**87%**	**11%**
Cologuard[108] Advanced Pre-Cancer	**57%**	**10%**
Grail Galleri[109] Stage I Colon Cancer	**43%**	**<1%**

What comes next?

University of Washington

UC San Francisco

UC San Diego

We're working with Kit and Trevor to put together a multi-institution U.S. validation study with 400 patients by providing funding and helping to bring in collaborators.

The initial results have been impressive, but they are from a small cohort in a single region. Maybe the algorithm just got lucky. Or the UK patients weren't a representative sample.

University of Chicago

To change clinical practice, we need more evidence from a larger, more diverse study.

It will also serve as a basis for the development of a test that can used in non-dysplastic colon samples.

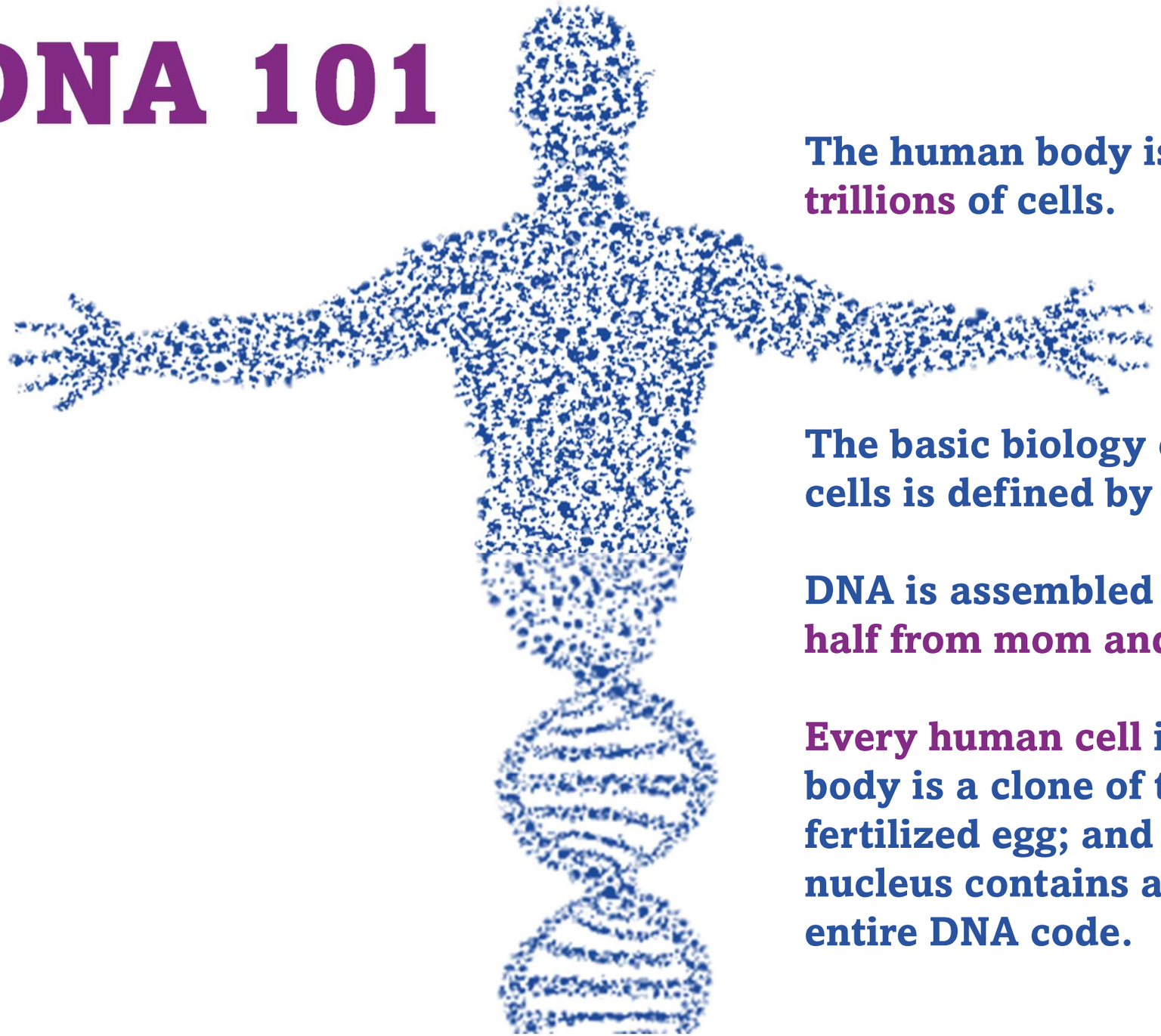
There's also reason to believe this work will help with the early detection of other cancers.

Want more detail on the molecular changes we're analyzing?

Read On!
(But it's not for everyone)

APPENDIX

DNA 101



The human body is made up of trillions of cells.

The basic biology of each person's cells is defined by their DNA.

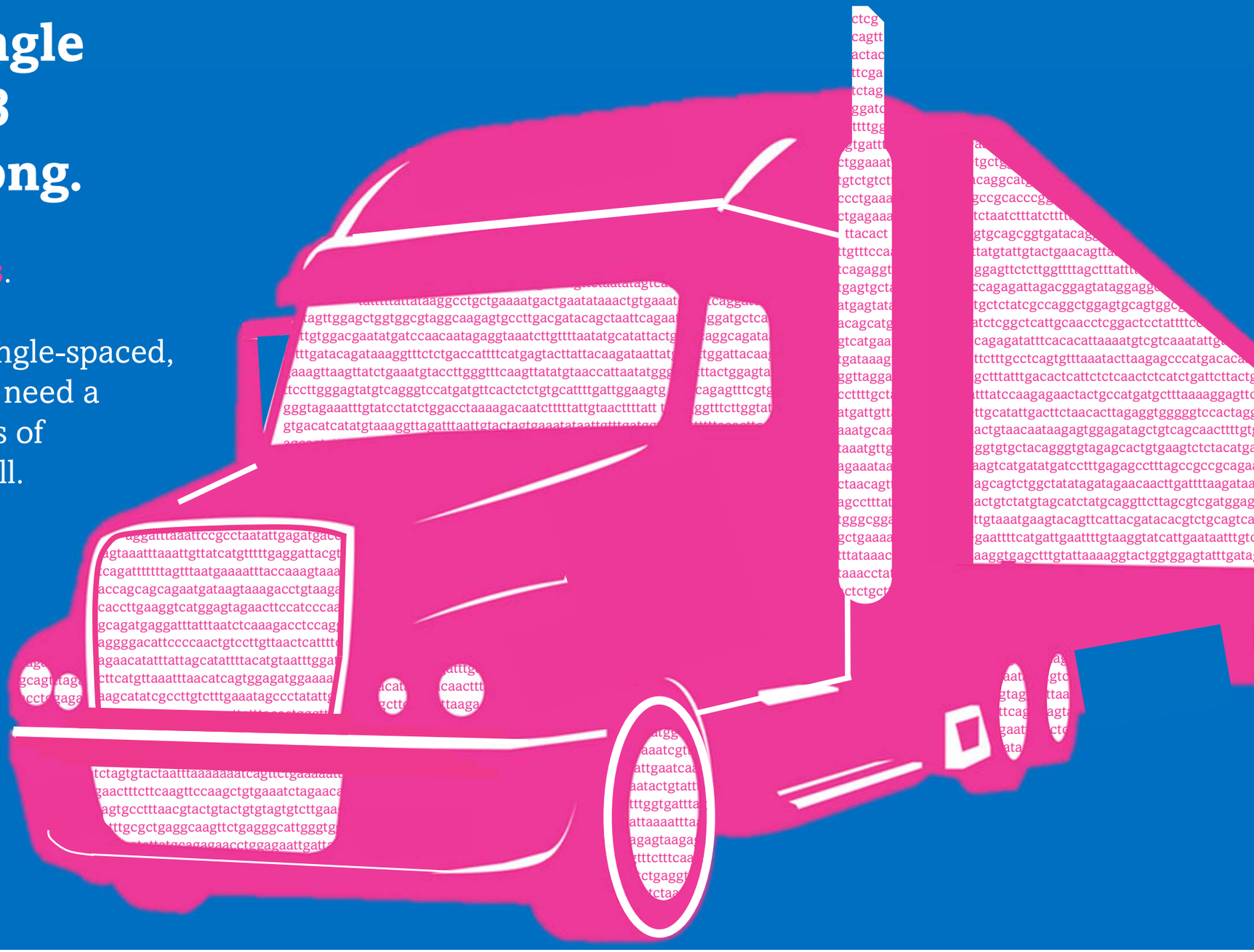
DNA is assembled at conception, half from mom and half from dad.

Every human cell in a person's body is a clone of their original fertilized egg; and every cell nucleus contains a full copy of the entire DNA code.

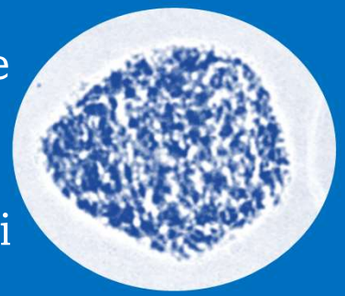
The DNA of a single human being is 3 billions letters long.

These letters are called **bases**.

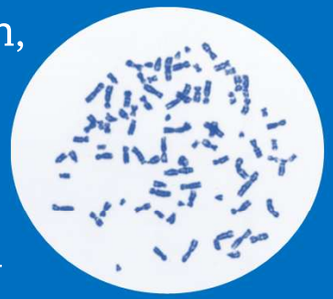
If you typed out your DNA, single-spaced, on 8 ½ x 11 paper, you would need a tractor trailer to carry the tens of thousands of pages it would fill.



Most of the time long strands of DNA fill the nucleus like a bowl of spaghetti



For cell division, DNA condenses into pairs of chromosomes, each carrying specific segments of DNA



If the DNA in a single human cell is laid out end-to-end, it is around 6 feet long

The double helix of DNA wraps around histones, which in turn coil into chromatin and chromosomes

23 and me

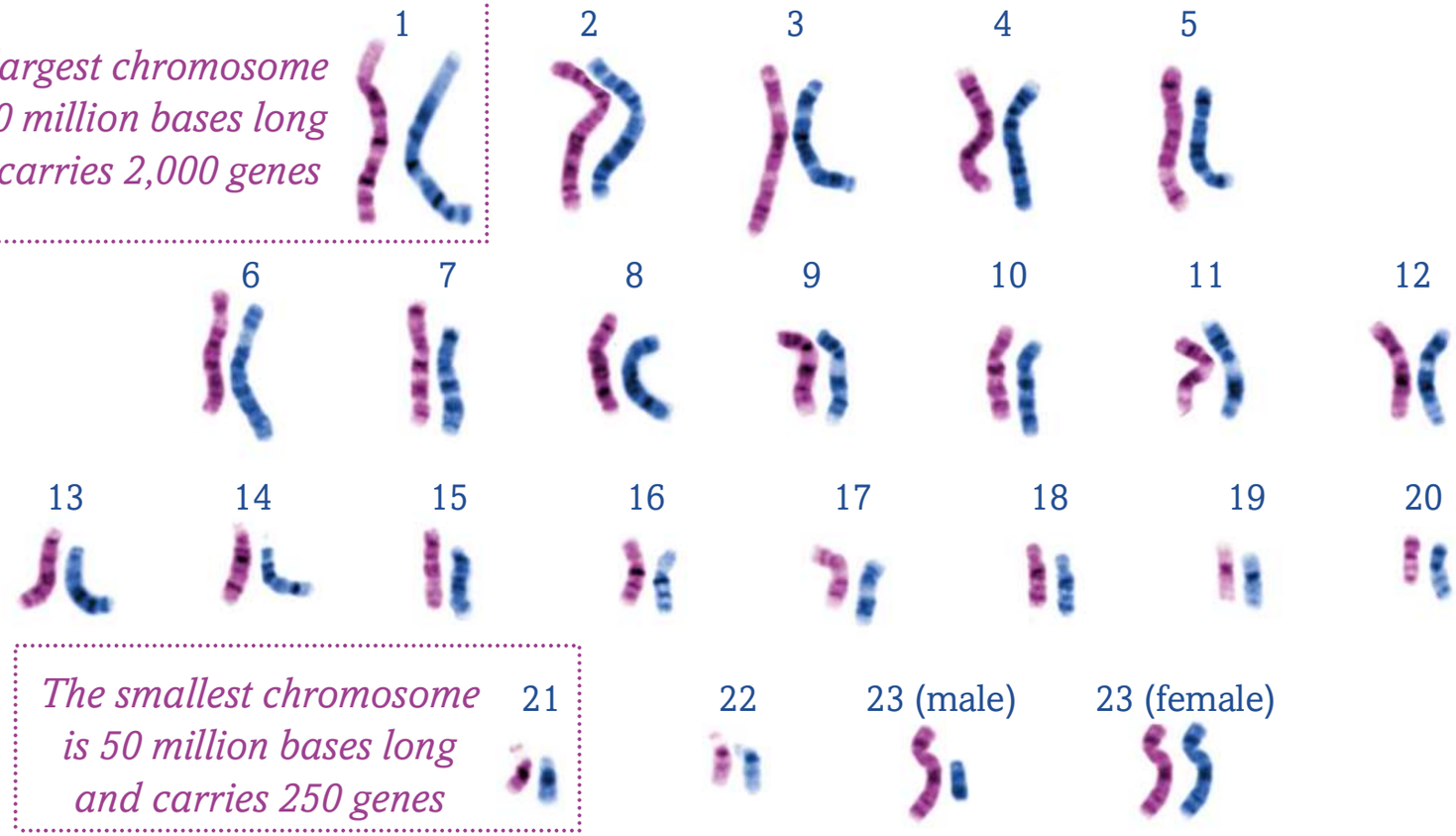
In humans, genes are carried on 23 chromosomes.

Genes are the templates for proteins, which are critical to how cells behave.

The length of an individual gene varies from a few hundred bases to more than 100,000 bases.

DNA Mutations alter the function of genes. Mutations can be as small as a single base change (e.g. A→T) on a single gene or as large as a scrambling of all 23 chromosomes.

The largest chromosome is 250 million bases long and carries 2,000 genes

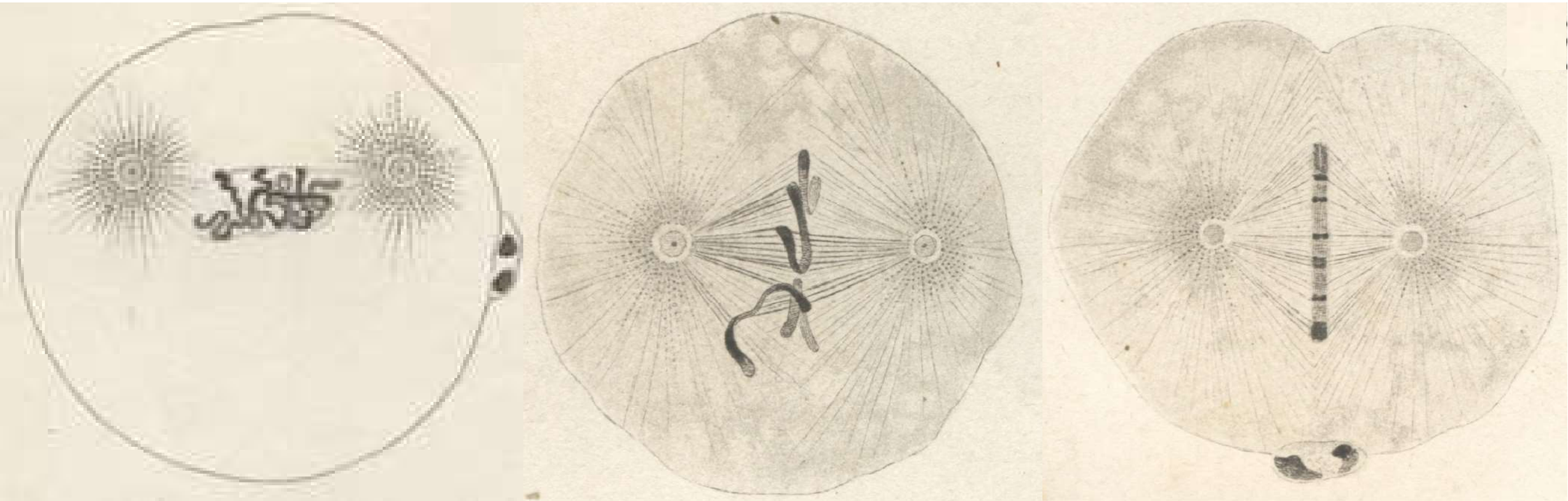


The smallest chromosome is 50 million bases long and carries 250 genes

Cell division

When a cell divides, its duplicated DNA lines up and splits evenly down the middle to ensure that each daughter receives a perfect set of chromosomes.

The drawings below – from 1887 – are among the earliest representations we have of cell division. They show the spaghetti-like nuclear DNA forming into chromosomes and being pulled into alignment by opposing microtubules to ensure even division.[110]



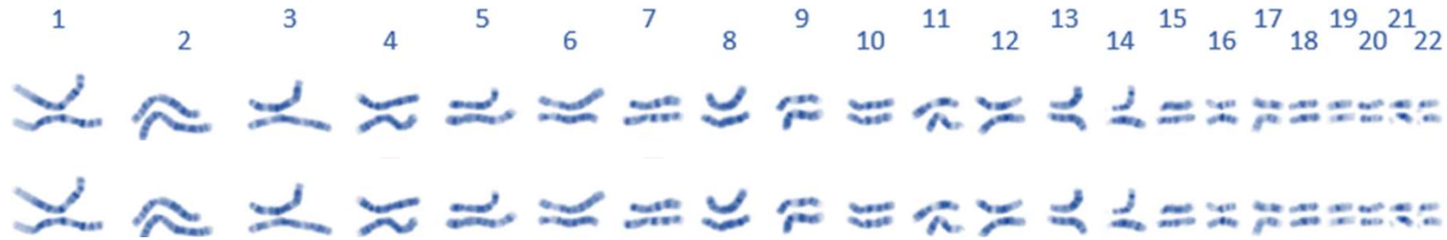
Aneuploidy

Chromosomes sometimes get stuck or broken during cell division, resulting in massive deviations from normal DNA quantities.

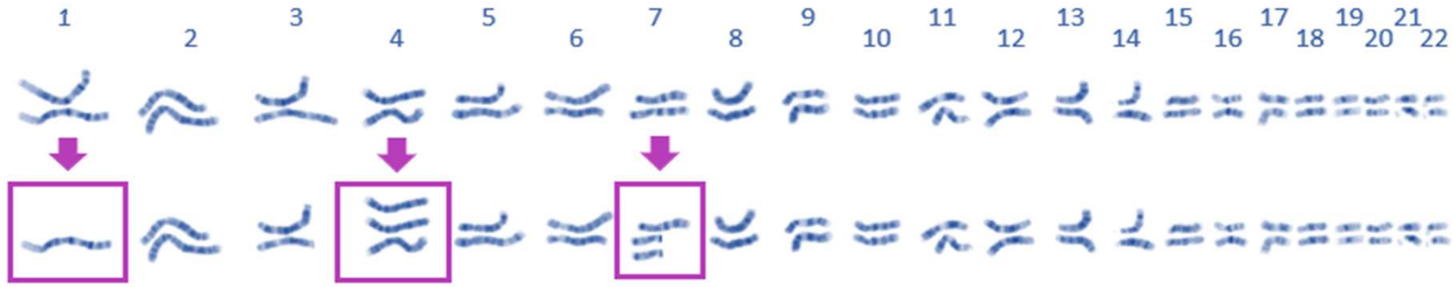
This type of mutation, called aneuploidy, is pervasive in cancer.

Aneuploid cells usually self-destruct or are cleared by other cells. But sometimes aneuploidy confers a competitive advantage by giving a cell extra DNA that enables uncontrolled growth, deleting DNA that prevents tumors, or a combination of both.[111]

Healthy Division



Aneuploid Division



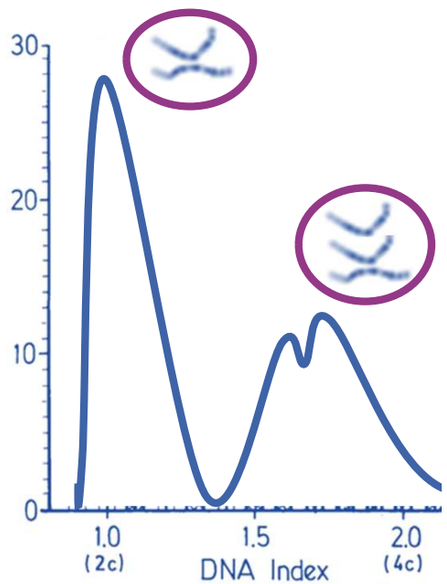
Aneuploidy in IBD

Aneuploidy occurs late in the process of developing typical colon cancer. Aneuploidy occurs early in IBD-related cancer, offering a clue for early detection.

In 1984, the year Amy was born, the first study of aneuploidy in IBD was published.[112]

Subsequent studies would confirm:

- Aneuploidy **typically precedes dysplasia** in the colon
- Aneuploid dysplasia is **more likely to progress** to cancer
- Aneuploidy **can often be detected more broadly** in the colon than visible dysplasia[21, 113]



Aneuploidy detection never took off for IBD cancer surveillance.

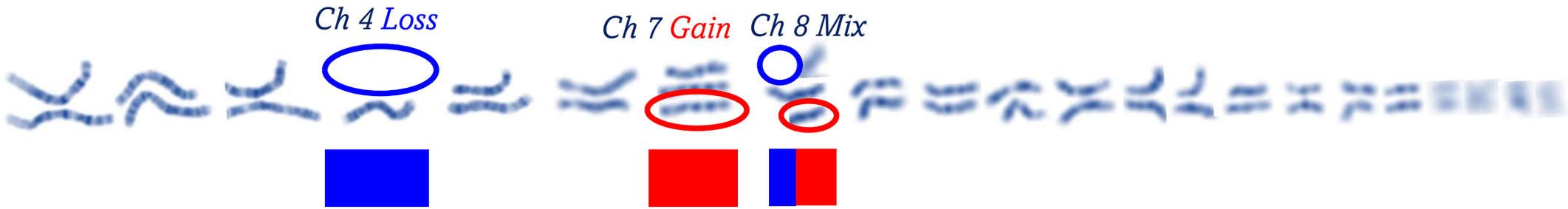
The tools of the era could identify the existence of aneuploid cells (the second hump in the chart), but it couldn't make useful enough predictions about what they meant.

That would need to wait for a superior technology.

Molecular resolution

Today's sequencing technology grabs fragments of DNA and parses them to find the specific areas where there are extra copies of DNA (gain) or missing copies of DNA (loss).

The length and location of **copy number** gains and losses are plotted from the start of the 1st chromosome (on the far left) to the end of the 23rd chromosome (on the far right):

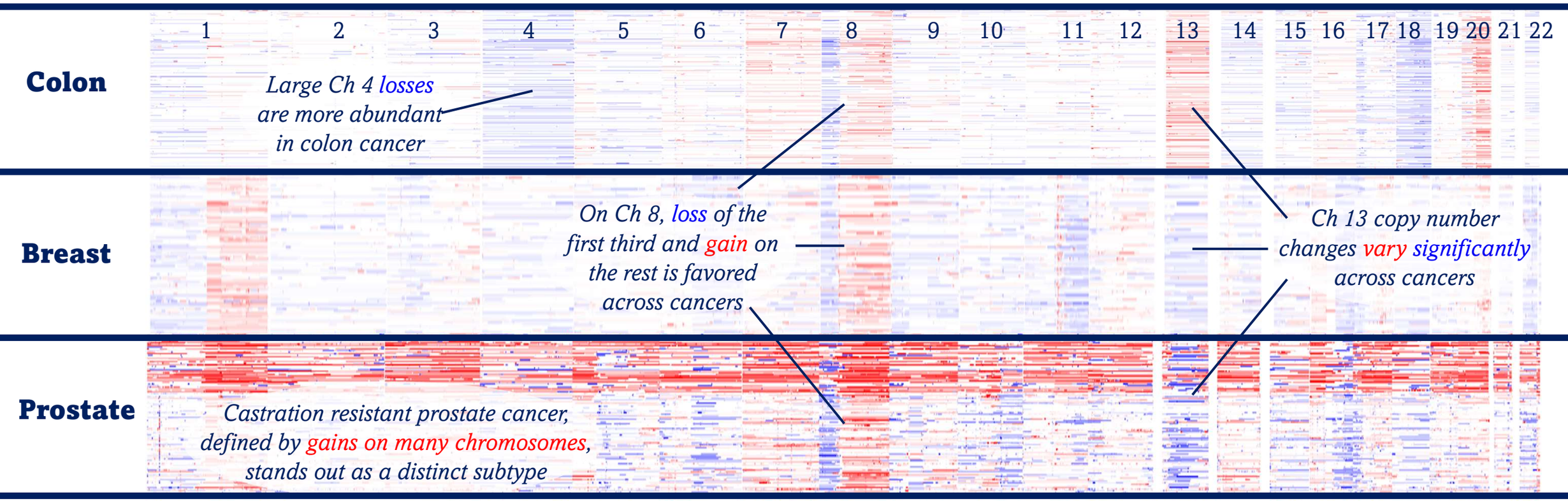


In a real colon cancer, we see a much more fragmented genome than in the previous example:

2 million bases long

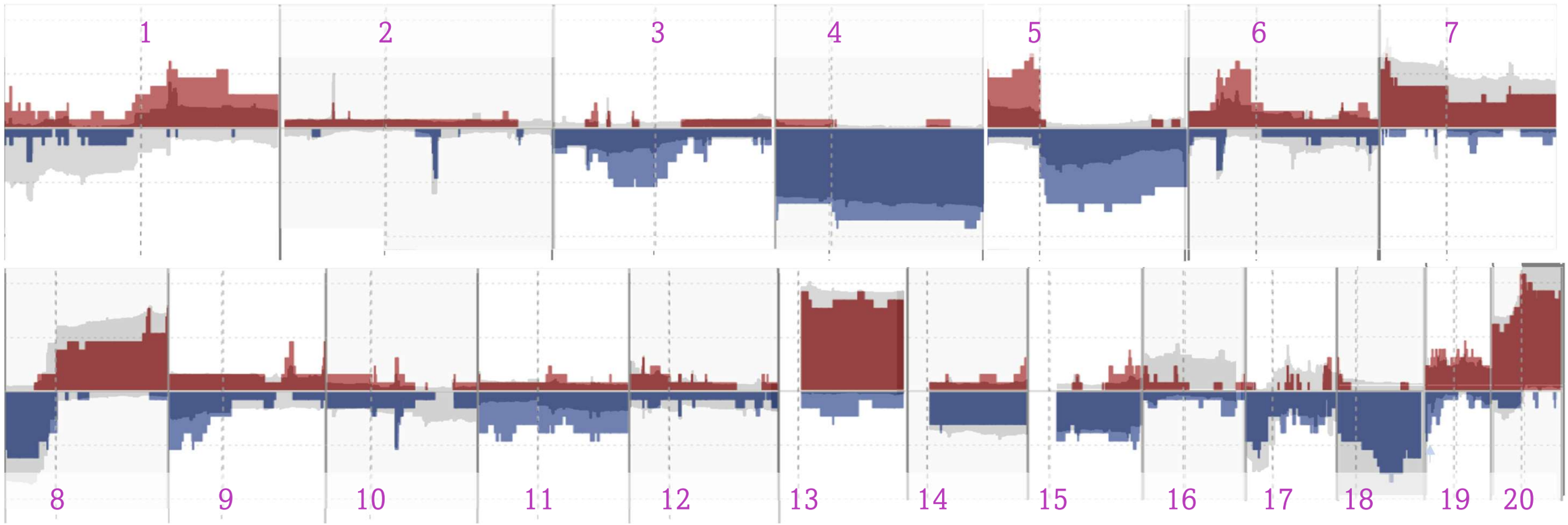
Looking across many patients, we see patterns of gains and losses reflecting a process of natural selection among cells.

Copy number changes occur **randomly** through errors in cell division. It is highly improbable any given cell division will result in changes that confer a major **competitive advantage**, but with **billions of cells** undergoing **trillions of divisions** opportunities arise. Advantaged cells take over their local environment and eventually spread. The patterns of gains and losses we see reflect the diverse genetic contexts in different parts of the body.[102, 114]



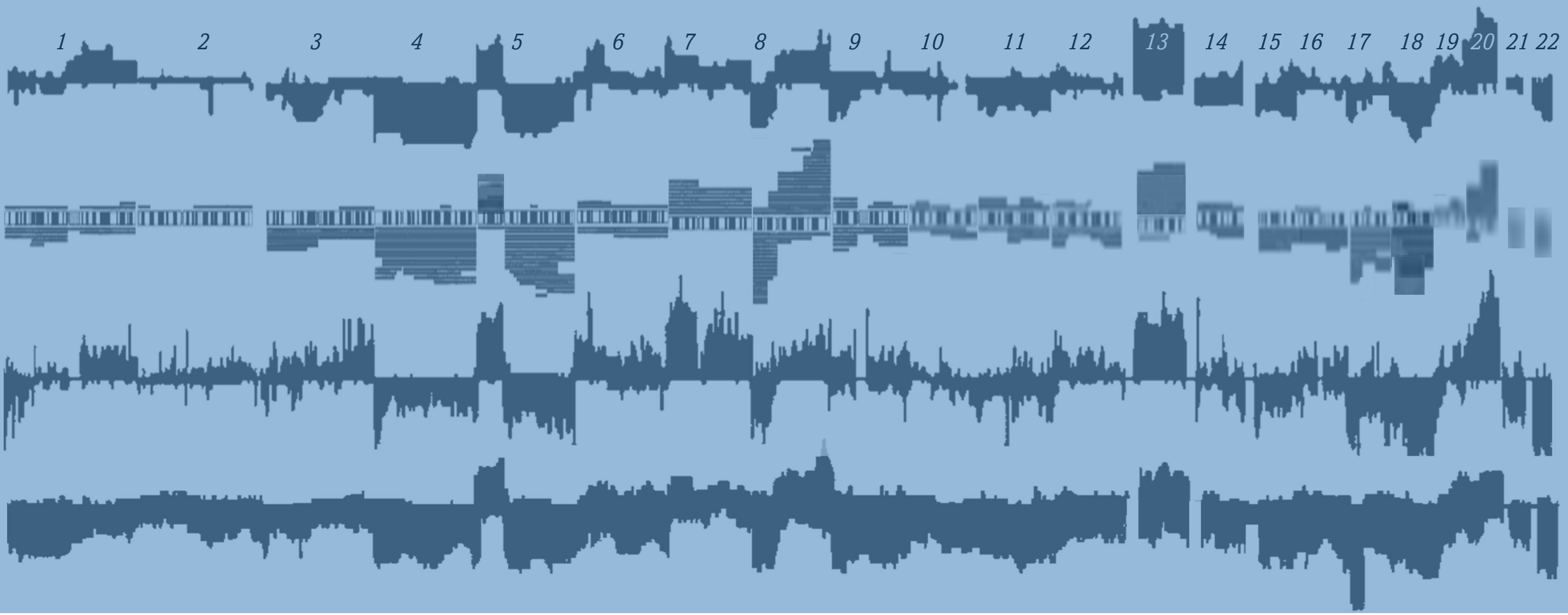
IBD cancer is different

An alternative to looking at many individual lines of patient data is to collapse them into a chart. This allows us to look at the frequency of gains and losses across a group of patients to identify the most common gains and losses in that population of patients. Below, frequency plots of IBD-related cancer (in color) are compared with typical colon cancer (gray overlay) highlighting the different copy number changes that have been "selected" because of the competitive fitness advantage they provide the cancer.[115]



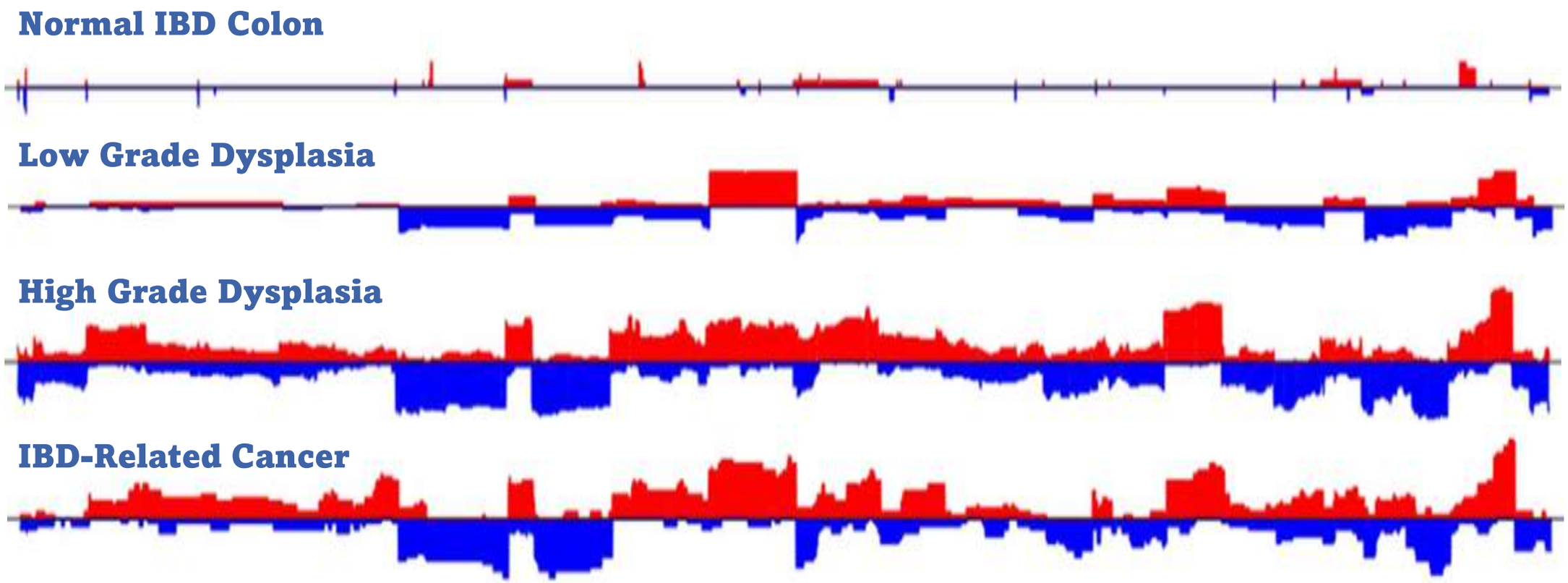
Consistent patterns

The distinct aneuploidy of IBD cancer have been consistently identified in studies over the past decades.[48, 115-119]
This is the “fingerprint” or molecular signature of IBD-related cancer.



From colitis to cancer

Kit and Trevor's group started by analyzing patient samples from normal, dysplastic, and cancerous tissue in IBD patients to identify patterns of cellular DNA changes (below). Further analysis of additional samples has allowed them to more precisely identify the pattern of DNA changes on the path to cancer.[88, 102]



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