What's Up With TAT?

(TAT: Testing Turn-Around-Time)

Tackling Cancer Genomic Testing Inequities in Ontario

CAPT 2024 CONFERENCE

MONDAY, OCTOBER 21, 2024

MaRS DISTRICT

9:30 – 10:30 A.M.

TORONTO

Meet Our Panel Experts

Mr. Steve Slack
Stage IV CRC Survivor,
Patient Advocate

Dr. Bryan Lo
Molecular Pathologist &
Assistant Professor, Ottawa
Hospital, Division of
Anatomical Pathology

Dr. Ken Craddock
Molecular Pathologist,
Sunnybrook Health
Sciences Centre

Dr. Michael Raphael
Medical Oncologist,
Odette Cancer Centre,
Sunnybrook Health
Sciences Centre

Why are we Here Today?

Introduction

A good problem…

Biomarker testing is growing:
Over past decade biomarker testing has expanded & led to improvements in patient outcomes.

The Challenge:
Increased demand is leading to delays in results & treatment, potentially leading to negative patient outcomes.

The TAT Problem: Medical Oncology Perspective

Example of the TAT Problem:
A Medical Oncology Perspective

THE 4% PROBLEM…

In patients with metastatic non-small cell lung cancer, an average of **4%** of patients will die during each week that passes without initiation of systemic therapy[1].

Mortality rates if therapy were delayed by X weeks[1]:

- 1 week: **4%**
- 2 weeks: **7%**
- 3 weeks: **10%**
- 4 weeks: **13%**

1. Stewart DJ et al, Cancer Med. 2021;10:9040–9046. doi:10.1002/cam4.4411

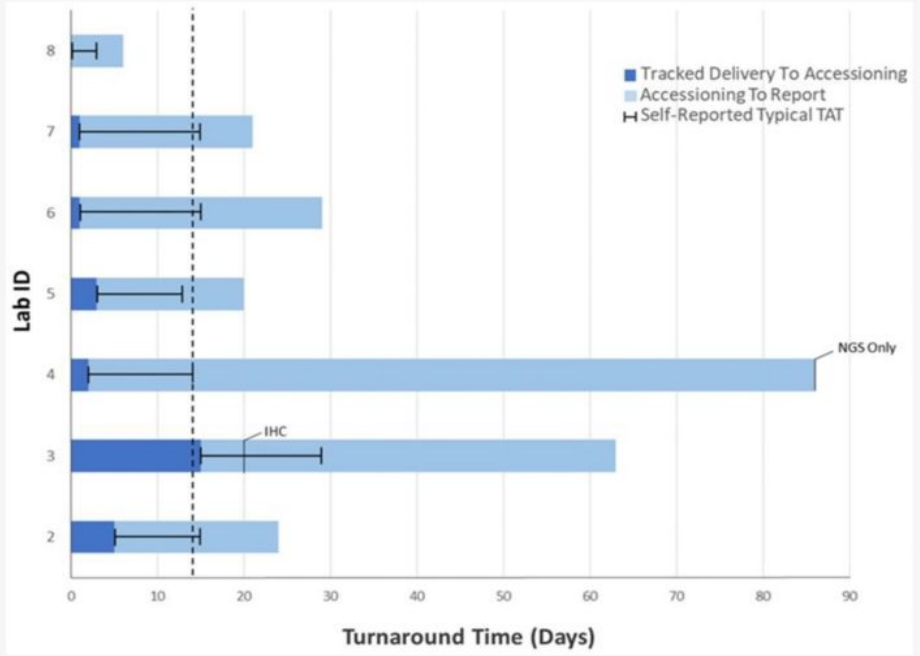
The TAT Problem: Pathology Perspective

Study nicely highlighting the urgency of improving the biomarker testing TAT

EXAMPLE OF THE TAT PROBLEM: Pathology Perspective

Key insight: 88% (7/8) of sites exceeded the recommended TAT of 14 days!

Figure 2. Total turnaround time (TAT) of participating laboratories. TAT measured from date of courier delivery to submission of all 3 reports (dark and light blue bar). Time from delivery to accessioning is shown in dark blue. Time from accessioning to final report is shown in light blue. Black bars indicate participant's self-reported typical TAT from the accompanying survey questionnaire. Dashed line shows 14-day mark, representing the recommended time to receive results from receipt in a testing facility. *IHC—IHC results were submitted separately. NGS only—only NGS reports were submitted.*



Bisson, K.R.; Won, J.R.; Beharry, A.; Carter, M.D.; Dudani, S.; Garratt, J.G.; Loree, J.M.; Snow, S.; Yip, S.; Sheffield, B.S. Novel Approach to Proficiency Testing Highlights Key Practice Variations in Cancer Biomarker Delivery. *J. Mol. Pathol.* **2024**, *5*, 1-10. https://doi.org/10.3390/jmp5010001

The TAT Problem: The Patient Perspective

CCRAN's June 2023 Biomarker Conference

Colorectal	Lung	Breast	Gastric
Ovarian	Endometrial	Cervical	Melanoma
GIST	Thyroid	Pancreatic	HCC
Blood Cancers	Rare Cancers	Cholangio-carcinoma	

Top 3 Barriers/Challenges: Reported by Patient Advocacy Groups[1]

Inter and intra-provincial disparities

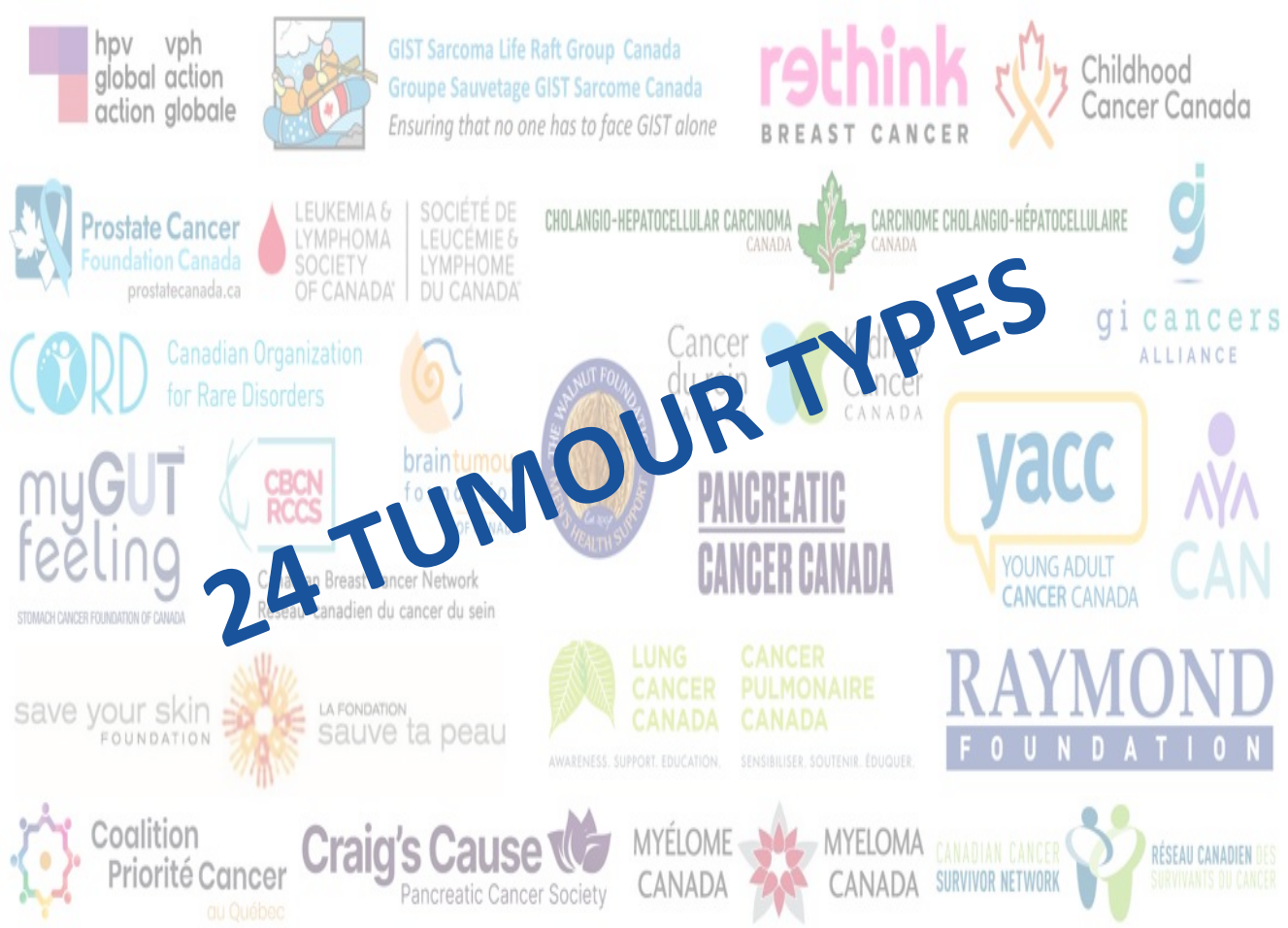
Lack of patient education

1. *Barriers/Challenges to Accessing Timely Biomarker Testing Results to Help Inform Treatment Decisions For Advanced Cancer Patients in Canada: CCRAN Biomarkers Conference*

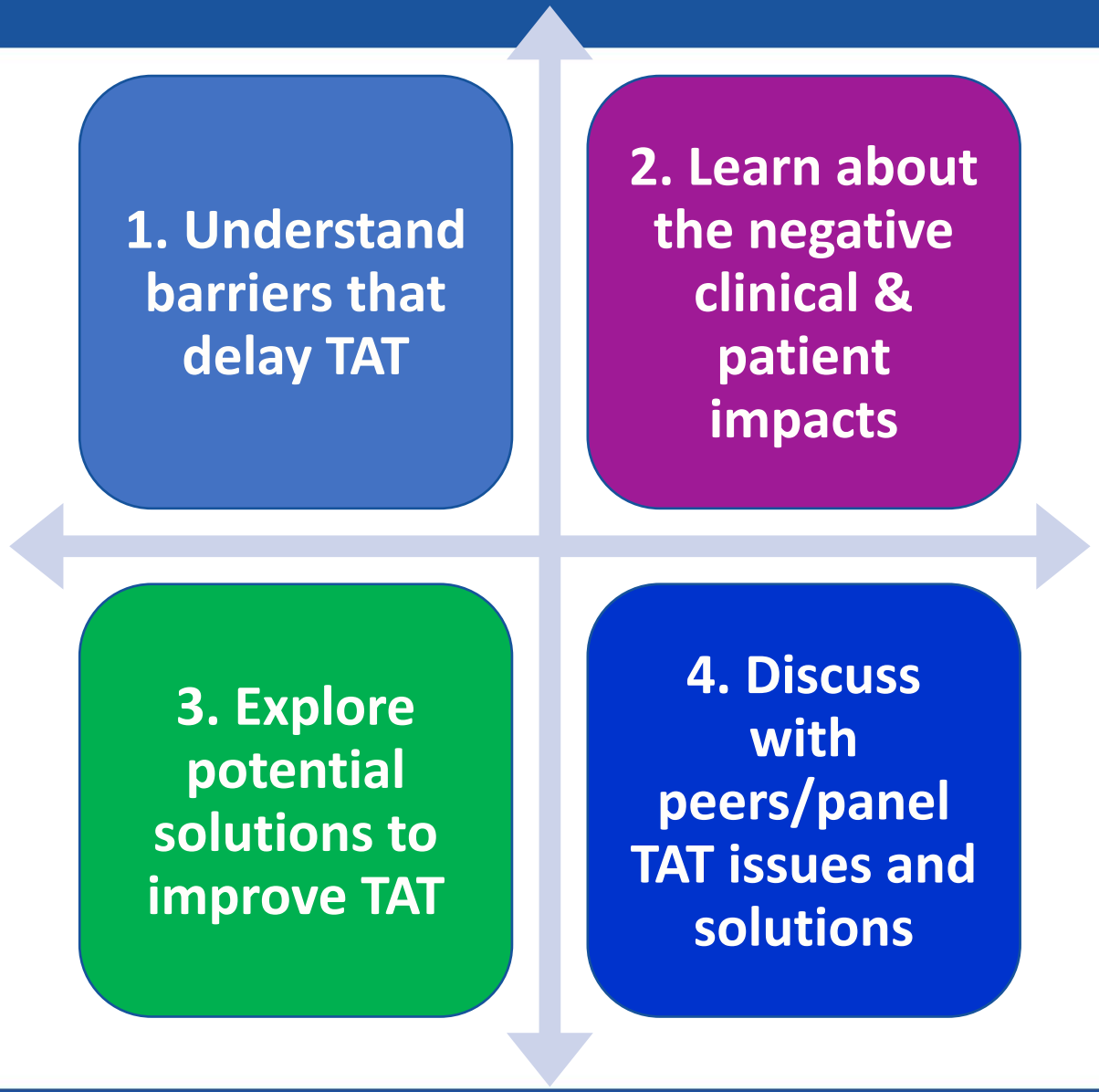
The Patient Perspective: CCRAN's 2024 Biomarkers Conference

CCRAN's Patient Survey Across 24 Tumor Types

1. **Delays in obtaining results**
2. **Biomarker testing is not routinely discussed with patients**
3. **Inter and intra-provincial barriers**



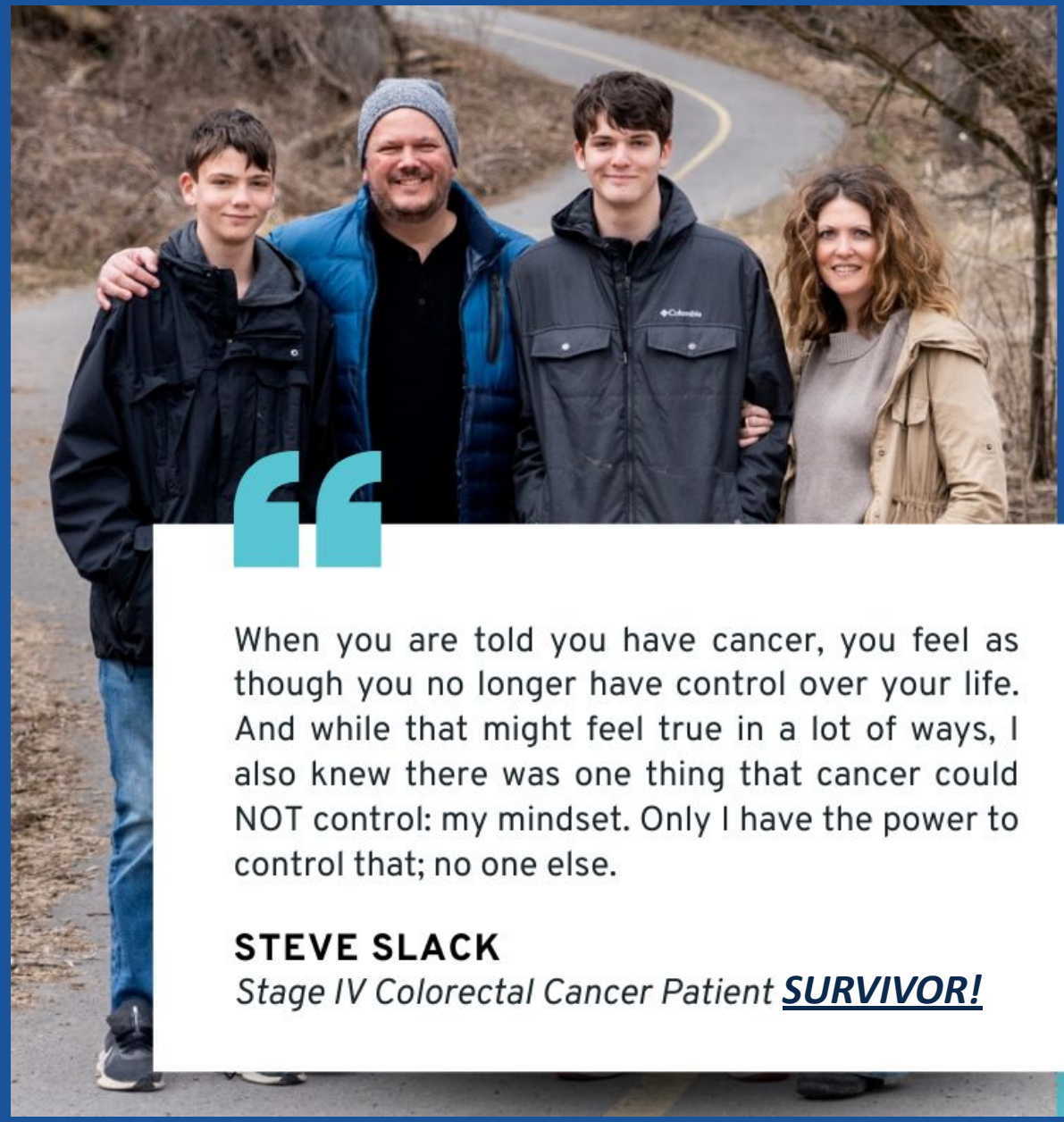
Session Objectives



The Patient Experience
(9:40-9:50 a.m.)

Meet Mr. Steve Slack –

Husband, Father, Son, Brother, Friend….& Patient Advocate



When you are told you have cancer, you feel as though you no longer have control over your life. And while that might feel true in a lot of ways, I also knew there was one thing that cancer could NOT control: my mindset. Only I have the power to control that; no one else.

STEVE SLACK
Stage IV Colorectal Cancer Patient ***SURVIVOR!***

Steve's Journey (9:40 – 9:50 a.m.)

June 2021 — Sigmoid Colon Cancer and 23 liver metastases. Sigmoid colon cancer resected.

Aug 24/21 — Ordered biomarker testing and paid for Foundation One ($3500).
August 31, 2021: Started biweekly FOLFIRI without targeted/precision medicine.

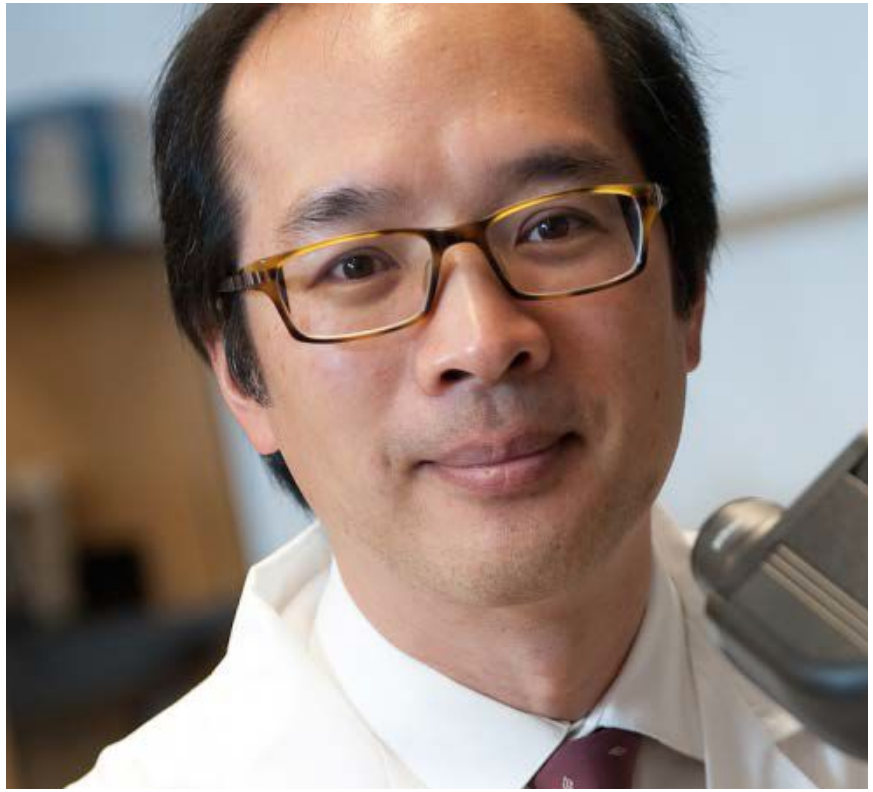
Oct 26/21 — Panitumumab added to FOLFIRI based on biomarker testing results - two months after initiation of systemic therapy.

Mar 2022 — HAIP Chemotherapy at SBK till September 2022. Eventually: one unresectable liver metastasis.

Apr 2023 — Eligible for Living Donor Liver Transplant Program. Restarted FOLFIRI + Panitumumab in May 2023 - October 2023 and started the process to seek out a live donor.

Nov 27/23 — Highly successful living donor liver transplant and TODAY IS NO EVIDENCE OF DISEASE.

The Problem with TAT? A Pathology Perspective (9:50 – 10:05 a.m.)



Dr. Bryan Lo
Molecular Pathologist & Assistant Professor,
Ottawa Hospital, Division of Anatomical Pathology

Dr. Ken Craddock
Molecular Pathologist, Sunnybrook
Health Sciences Centre

Is there a problem with TAT?

A Pathology Perspective (9:50 – 10:05 a.m.)

PART 1: A real-world journey

Ken Craddock

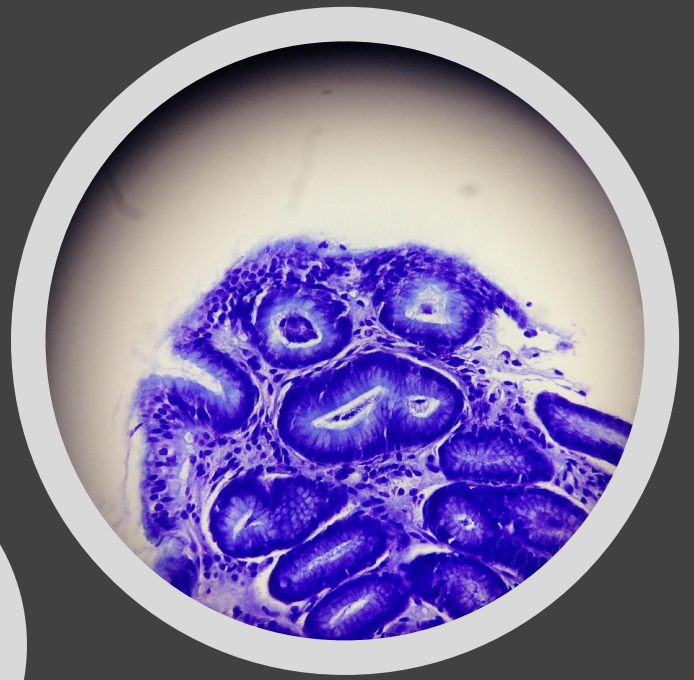
The journey a test takes from surgery to a report

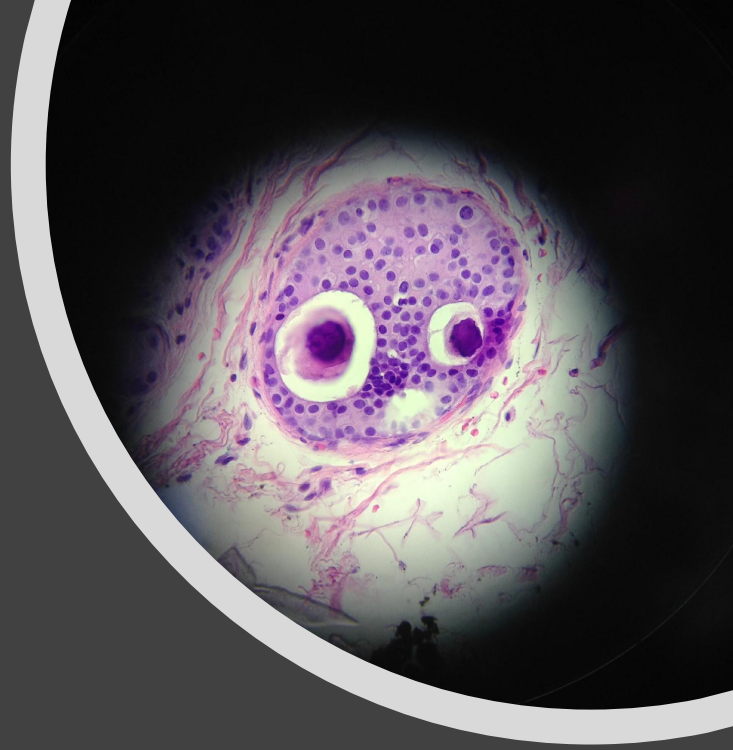
Explore ideas on where we could improve on TAT

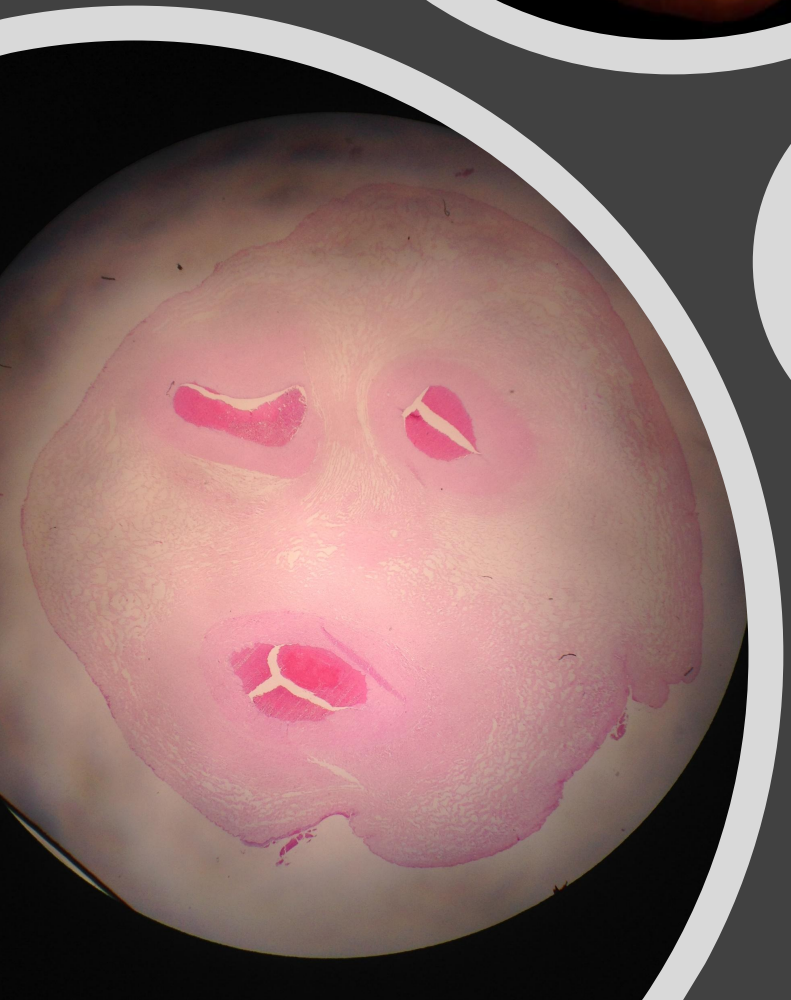
PART 2: Lessons in TAT

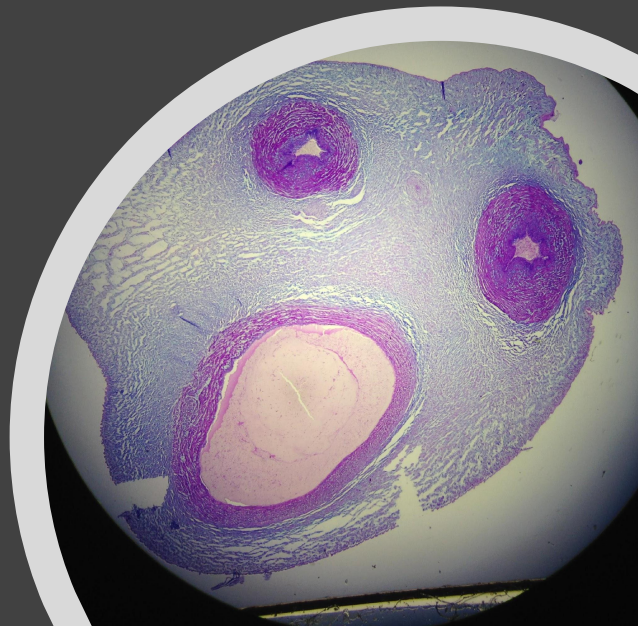
Bryan Lo

Review informal assessments of TAT patterns from a center that services a large community region



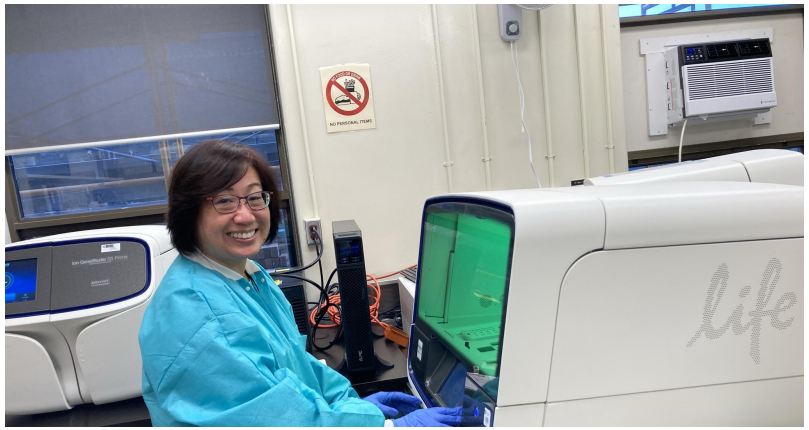


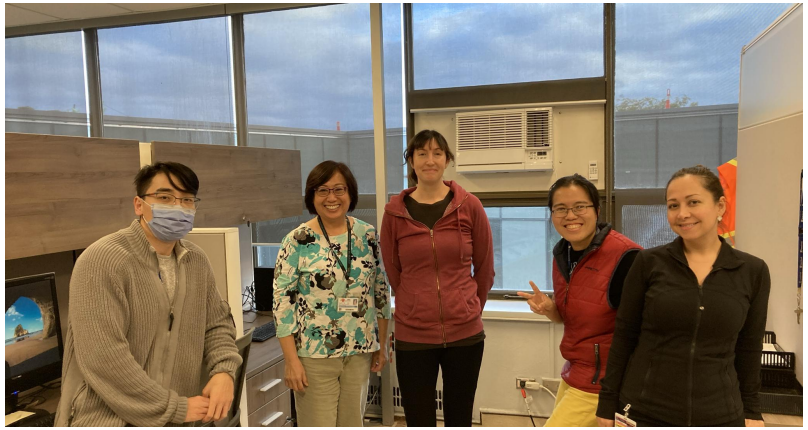


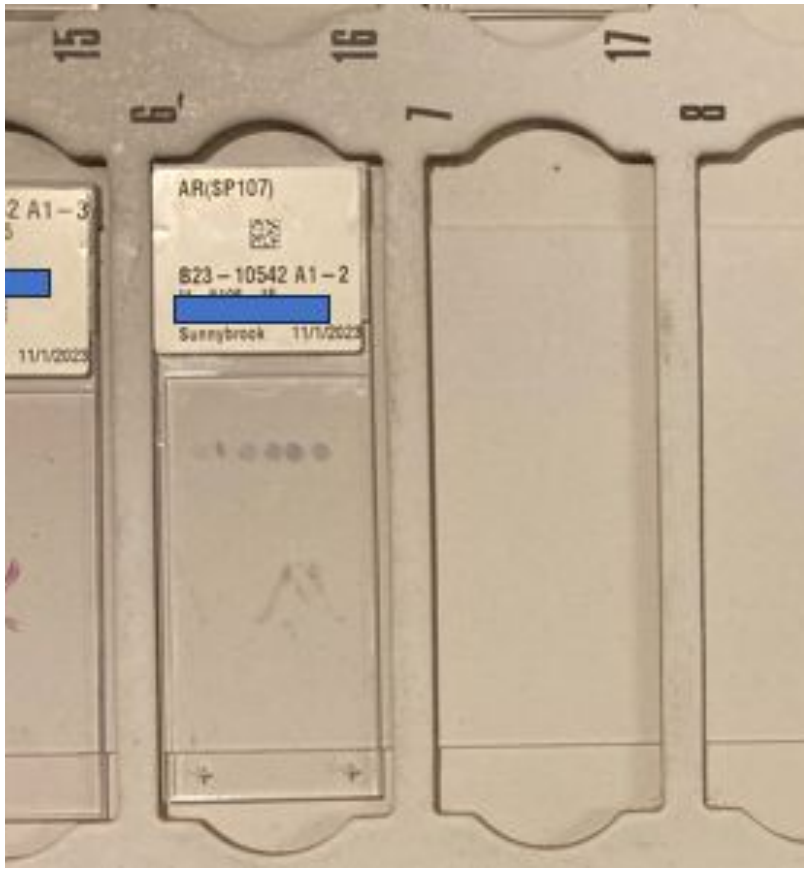


Turnaround Time (TAT)
Cancer Molecular Biomarkers

Dr. Ken Craddock, MD FRCPC (Pathology)
FCCMG (Cytogenetics & Molecular Genetics)
Molecular Pathologist, Sunnybrook







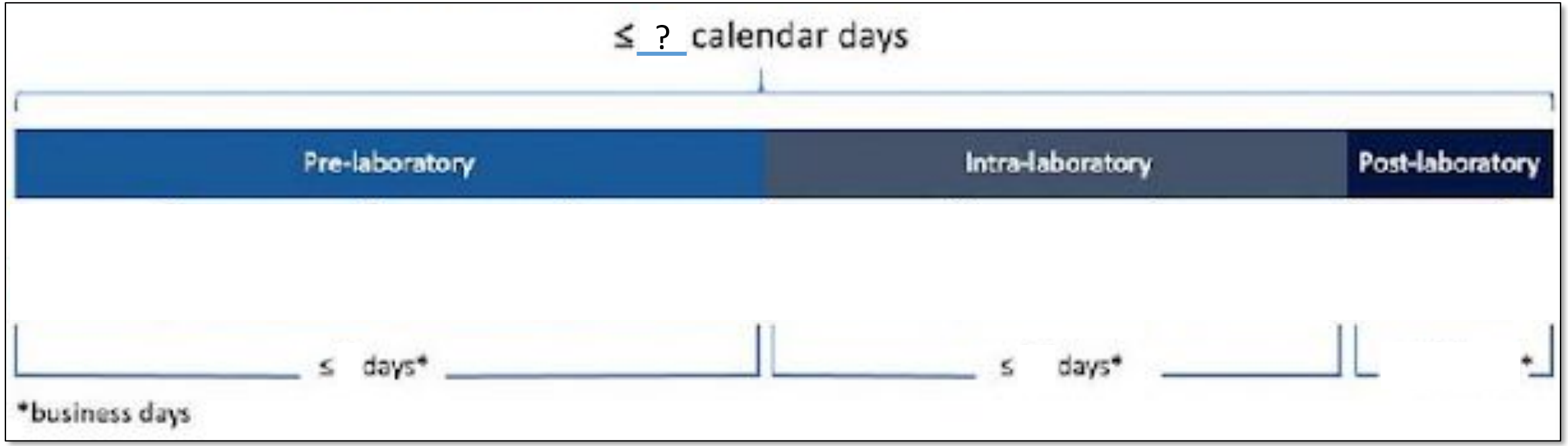
Journey into a “little-known” Real-World Process

Molecular Biomarker Testing Process

Example in Lung Cancer: 2020 Canadian Consensus Recommendations

Sunnybrook HEALTH SCIENCES CENTRE

How long would you expect this process be recommended to take?



Cheema P, *et al*., *Curr Oncol*. 2020;27(6):321-329.

Molecular Biomarker Testing Process

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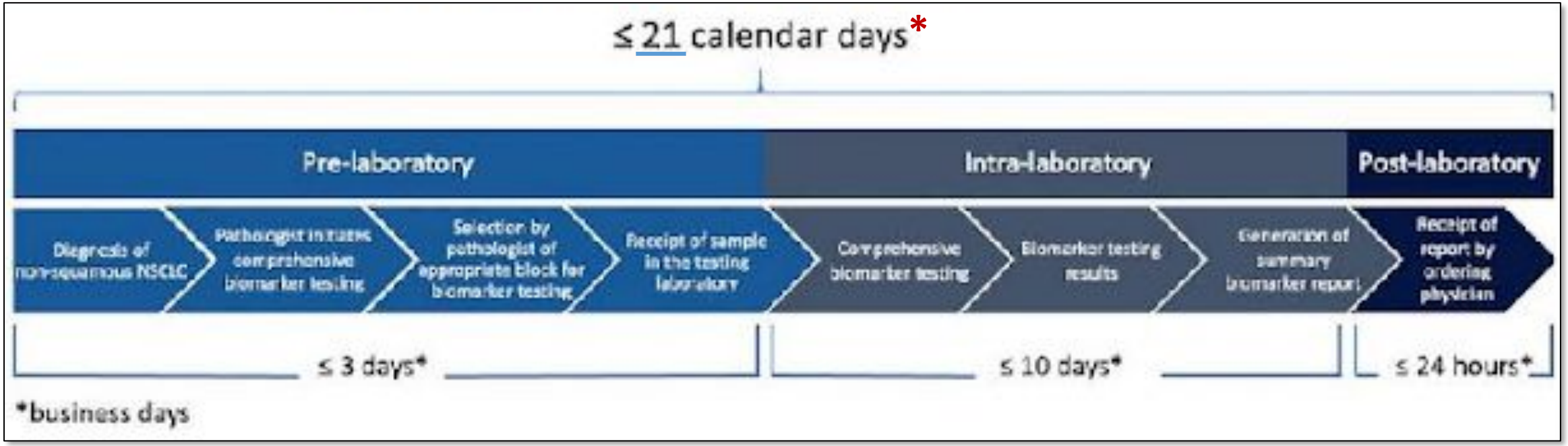

*from diagnosis / test order = **that's ~15 business days!**

Cheema P, *et al.*, *Curr Oncol*. 2020;27(6):321-329.

Sunnybrook Molecular Biomarker Testing Process

Sunnybrook HEALTH SCIENCES CENTRE

Pre-laboratory | Intra-laboratory | Post-laboratory

Pre-lab 3-10+ days

- Day 0 biopsy
- 2-5 days diagnosis of cancer & test order*/block selection
- 0-5 days[1] retrieval of block(s) & send out
- 0-3 days transportation to testing centre

Note: all days expressed in business days and TAT depend on send-out frequency

Sunnybrook Molecular Biomarker Testing Process

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Prep 2-10+ days

- 0-2 days case accessioning & pathologist order
- 1-5 days slide prep (histo lab, IHC)
- 1-2 days DNA/RNA extraction adequate
- 2-5 days DNA/RNA inadequate

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Note: all days expressed in business days and TAT depend on send-out frequency

Sunnybrook Molecular Biomarker Testing Process

Sunnybrook HEALTH SCIENCES CENTRE

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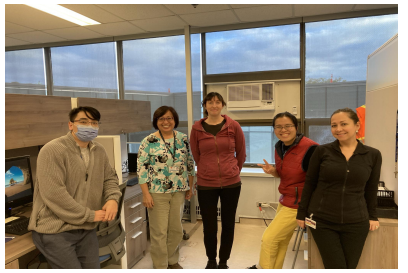
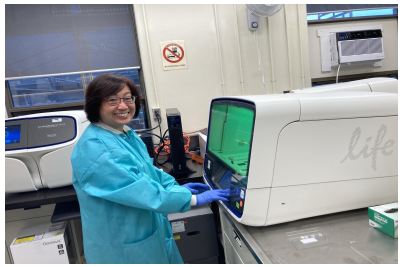
NGS Lab 7-10 days

- Macrodissection
- DNA extraction
- Library Preparation
- Sequencing
- Variants detected are assessed by genome analyst
- Molecular pathologist reviews and completes assessment





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Sunnybrook Molecular Biomarker Testing Process

Sunnybrook HEALTH SCIENCES CENTRE

Pre-laboratory | **Intra-laboratory** | **Post-laboratory**

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SUNNYBROOK HEALTH SCIENCES CENTRE
University of Toronto
2075 Bayview Avenue, Toronto, Ontario M4N 3M5
(416) 480-6100 ext. 4600 fax (416) 480-4271

Addendum

Patient:
HFN:
Account #:
TSRCC #:
OHIN #:
DOB/SEX:
Patient Address:

Accession #: B23-2040
Location: TBC
Date of Procedure: 02/27/2023
Date of Receipt: 03/06/2023 13:58
Date of Report: 03/24/2023 16:38

Physician:
Copies to:

CLINICAL INFORMATION

SPECIMEN(S) SUBMITTED
A: Small bowel, ovary and tube (S23-3602)

PROCEDURES/ADDENDA
Addendum Diagnosis

OVARIAN CANCER BIOMARKER RESULTS:
- Clinically actionable (Tier 1) variant detected:
  - BRCA2 NM_000059.4:c.3545_3546del (p.Phe1182*) (VAF:92%)

Interpretation:
BRCA2 loss of function mutations are recurrently identified in ~10% of high-grade ovarian carcinomas, and are associated with response to molecularly targeted therapies such as PARP inhibitors. The p.Phe1182* has been recurrently described in patients with hereditary breast and ovarian cancer (HBOC), and has been classified as pathogenic by the ClinGen-approved ENIGMA expert panel.

Please note that this test does not distinguish between germline (hereditary) and somatic (acquired) mutations. A significant proportion (majority) of BRCA variants identified in ovarian cancers are of germline origin and this finding may impact the patient and their family members' future cancer risk. Referral for genetic counselling is indicated, if not already arranged, to initiate further investigation.

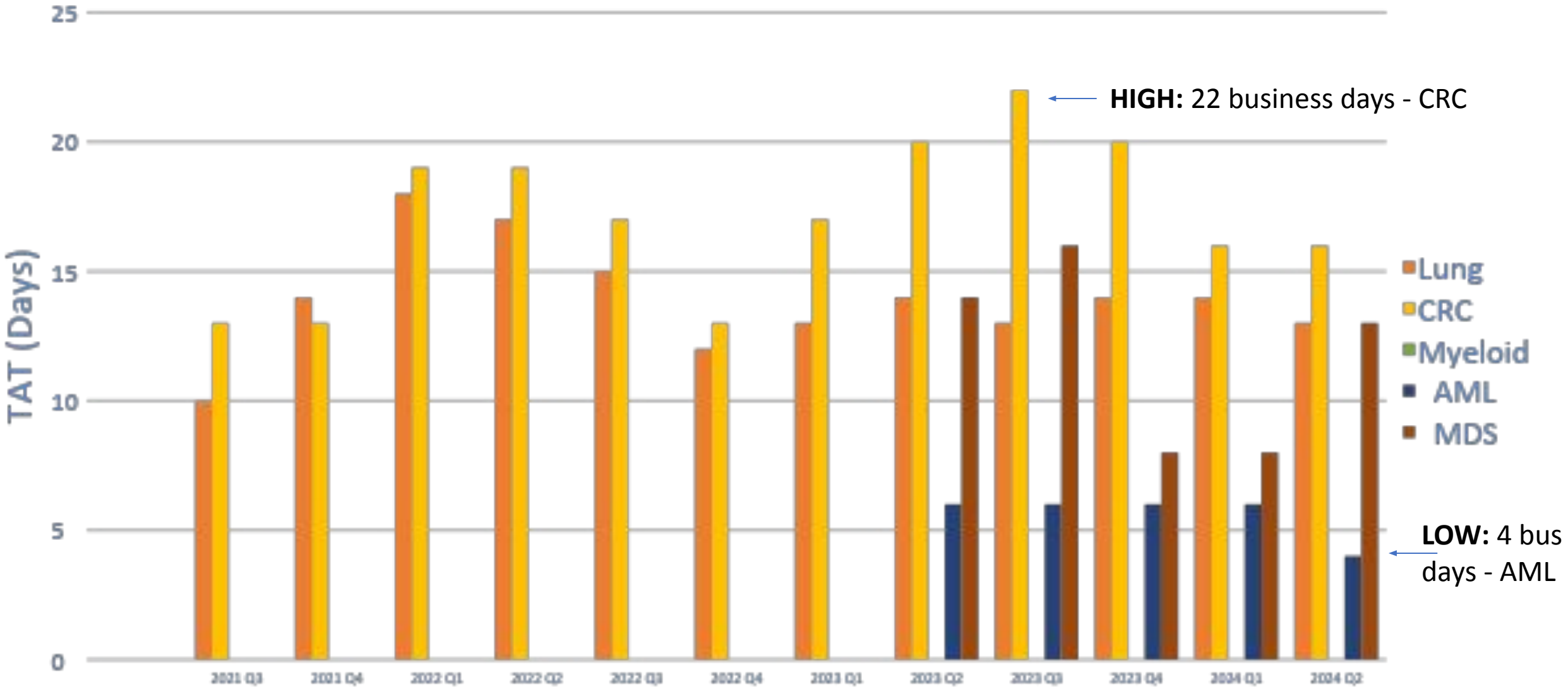
Genes (exons) analyzed and reported (HRR-DNA assay):
BRCA1 (full coding sequence), *BRCA2* (full coding sequence)

Final Report

- **Range:** 13 to 30 business days
- **Results:** Clinically actionable variant detected (or not)
- **Interpretation:** Supporting information for Tier assignment, Clinical utility of the result
- **Next:** Turn Around Time Assessments

Note: all days expressed in business days and TAT depend on send-out frequency

Sunnybrook Molecular Biomarker (NGS) Turnaround Times 2021-2024



TAT delays & challenges

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Lab staffing shortages
histology & molecular labs

Instrument & reagents gaps
problems requiring sample / run repeats

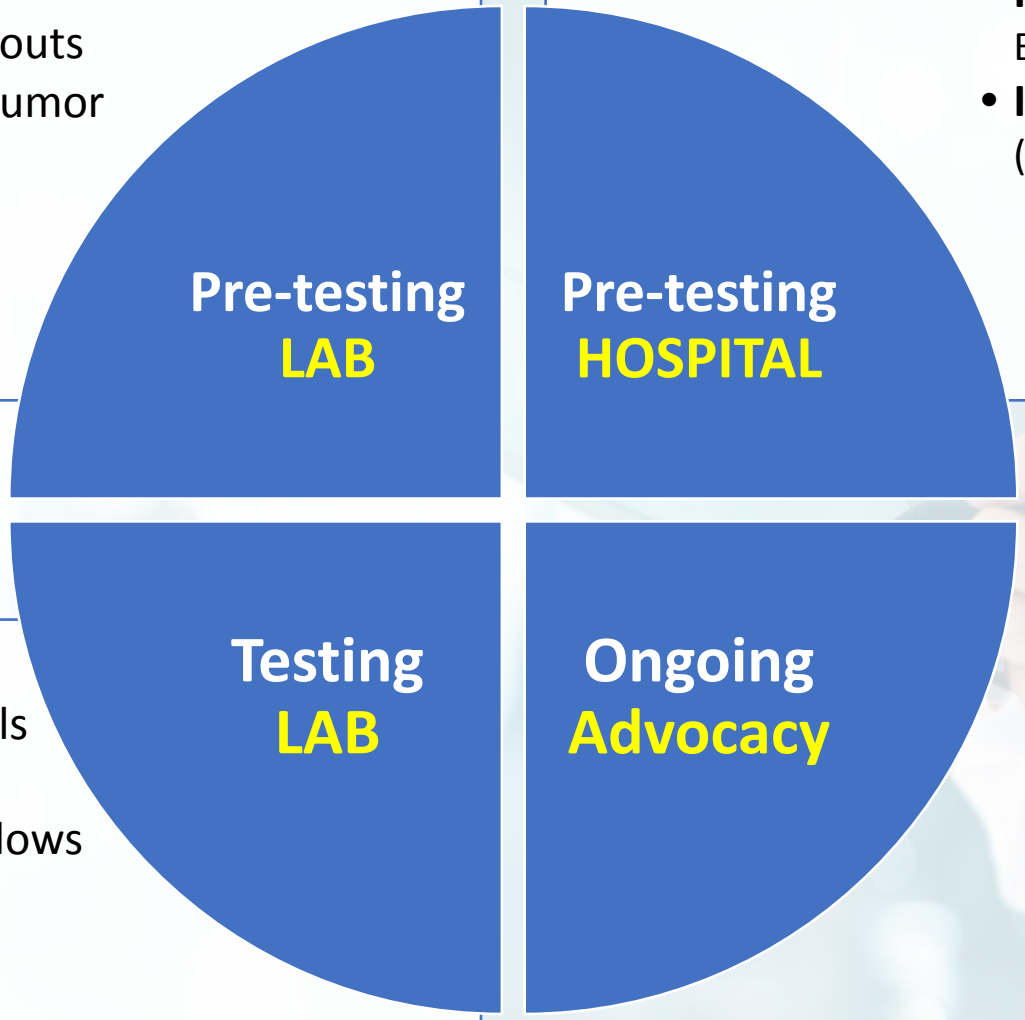
Rapid increase in volumes
testing indications & complexity (↑ genes)

Inadequate Case Delays
requesting additional material

Molecular Biomarker Testing:
Opportunities for Process Improvement/Optimization

Sunnybrook HEALTH SCIENCES CENTRE

- Expedite diagnosis for biopsies
- Optimize block retrieval, send-outs
- Reports which blocks contain tumor
- Daily vs. batched send-outs
- Same-day couriers
- Flag cases on test requisition



- **Increase tissue available:**
  Ex. Lung : 20-gauge, 4-5 passes
- **Improve small biopsy handling**
  (cores, endobronchial biopsies)
  - ✔ Divide into 3 blocks
  - ✔ Improve lung protocol - all blocks
  - ✔ Send best blocks up-front

Optimize several process

- Staffing levels & staffing models
- Histology workflows
- NGS testing & reporting workflows
- Improve access to reports

Molecular Biomarker Testing:
Opportunities for Process Improvement/Optimization

Sunnybrook HEALTH SCIENCES CENTRE

Advocate for:

(1) More adequate staffing levels in labs

- Administrative, technical, and medical staff
- Both pre-testing and testing labs
- Staff according to "peaks" in workload, not "average" workload

(2) Increase spends for send-outs from pre-testing labs

- Courier costs, as opposed to using free / cheap service that picks up in frequently and does not go directly to the testing lab

(3) Access to reports via Connecting Ontario

- Assistance to labs in IT challenges of connecting their LIS to OLIS
- Bioinformatics support to ensure reports are **easy to find** and **in a readable format**

Is there a problem with TAT?

A Pathology Perspective (9:50 – 10:05 a.m.)

PART 2: Lessons in TAT

Bryan Lo

Review informal assessments of TAT patterns from a center that services a large community region

Turnaround time challenges & opportunities:
A regional molecular testing approach

Bryan Lo
MD, PhD, FRCPC (Medical Genetics)
Molecular Oncology Diagnostics Lab
The Ottawa Hospital
Eastern Ontario Regional Laboratory Association

The Ottawa Hospital | L'Hôpital d'Ottawa

Disclosures

Bryan Lo has served on advisory boards for:

- AstraZeneca, Pfizer, Bayer, Novartis, Jansen and Roche
- Bryan Lo is the medical director for the Ottawa Molecular Oncology Diagnostics Laboratory which has received research and quality improvement grant support from Amgen, AstraZeneca, Roche and EMD Serono

Eastern Ontario Regional Laboratory Association

EORLA

EORLA is a member-based, non-profit organization serving the Champlain region of Eastern Ontario

18 member hospitals

1.4 million residents

14 million lab tests annually

750 Medical Laboratory Professionals, along with approximately 75 Medical/Scientific staff, 50 Administration Staff

What are the Benefits of doing Molecular Oncology Testing Locally?

- **Greater autonomy** on turn around time (TAT)
- **Optimization** and **stewardship** of required specimens for testing.
- **Collaboration** of local laboratory and clinical experts to optimize utilization of molecular testing and interpretation of results.

The Ottawa Hospital | L'Hôpital d'Ottawa

Molecular Oncology Diagnostics Laboratory (MODL)

- **Providing DNA/RNA tests** for solid tumors **since 2015** (coincided with Cancer Care Ontario funding initiative for EGFR testing in lung cancer)
- **2,500** Next Generation Sequencing assays each year
- **Majority of tests** are for **Ottawa** Hospital **specimens**
- **Minority** of cancer specimens tested are **other hospitals** in the Champlain region

The Ottawa Hospital | L'Hôpital d'Ottawa

The Ottawa Experience:

Sometimes multi-step processes can quickly be improved with technology

Ion Chef / Gene Studio S5
Launched 2021

Genexus
Launched in 2023

DNA/RNA quantitation → Library preparation → Template preparation → Sequencing → NGS QC → Variant calling → Variant annotation → Report generation

Consolidated process improved TAT

DNA/RNA quantitation → NGS → NGS QC → Variant calling → Variant annotation → Report generation

Shortened TAT?

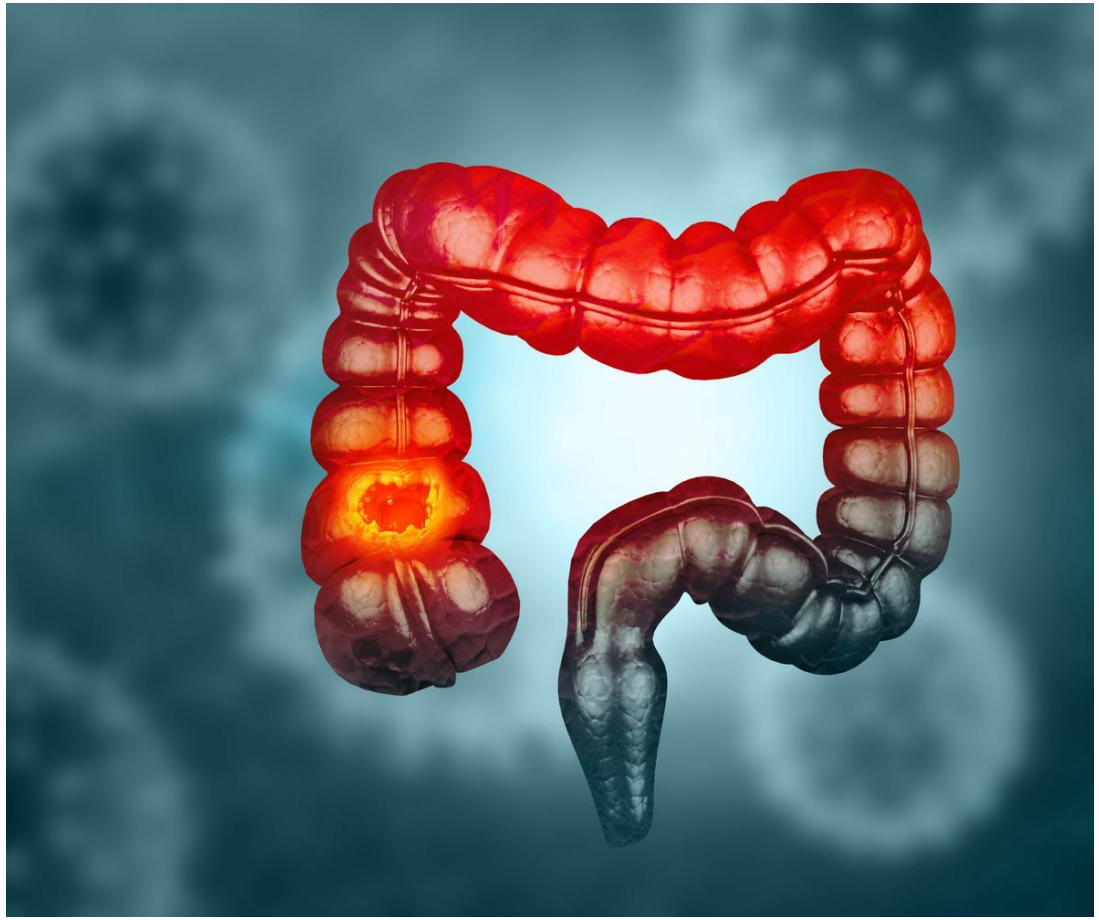
A TAT Case Study
NGS Turnaround times for Colorectal Cancer (CRC)

2 years ago MODL implemented a new lab information system (**EPIC Beaker**)

805 CRC NGS reports

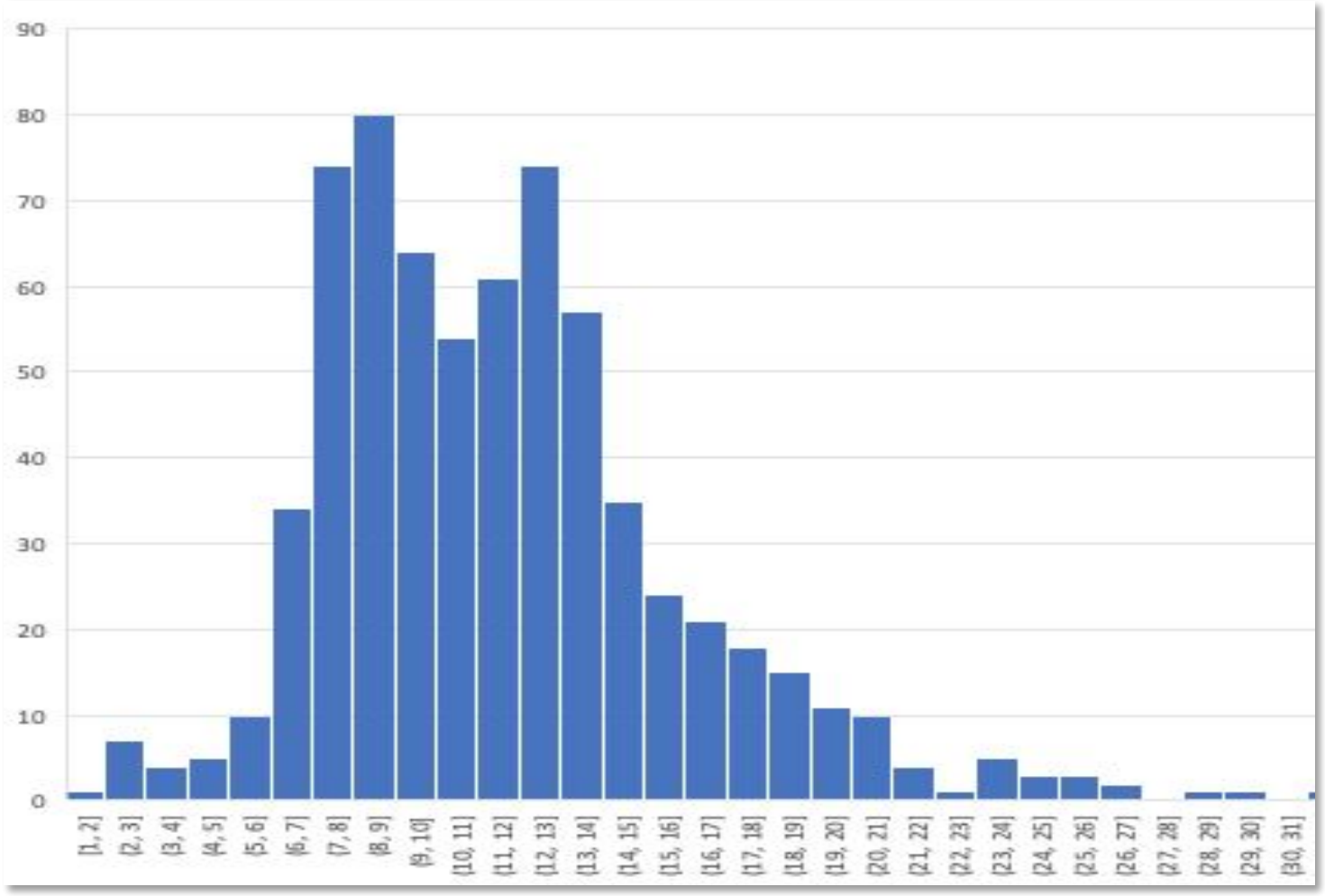
For Cancer Care Ontario, turnaround time (**TAT**) is calculated **from receipt of FFPE block to report sign out**

Average TAT is 12 calendar days (10 working days)



Is TAT Ok?

Is 12 calendar days lab TAT *acceptable?*

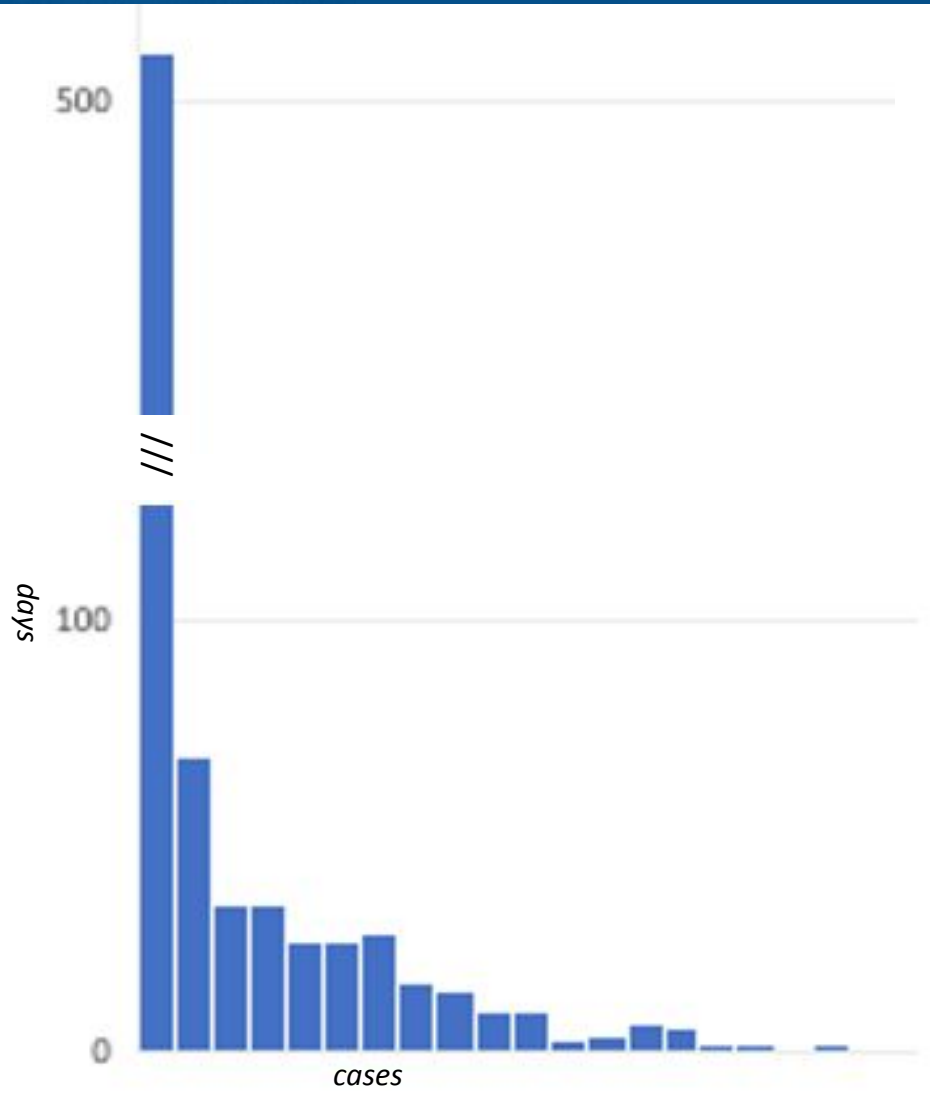


Test Turn Around Time (from lab receipt to report generation)

- **13%** are TATs **between 15-19 days**
- **5%** are TATs **>20 days**
- **Of** the **TATs >20 days** approximately **50%** are **due to technical repeats**
- And **SOME** other reasons…
  - ✔ *Some long TATs are due to **addition pathology review** after block receipt*
  - ✔ *Some long TATs are due **EPIC beaker implementation issues** and do not properly reflect the TAT*
  - ✔ *Some long TATs **need further investigation***

Delays Before NGS:

Test ordering → Pathology review → Block received in lab

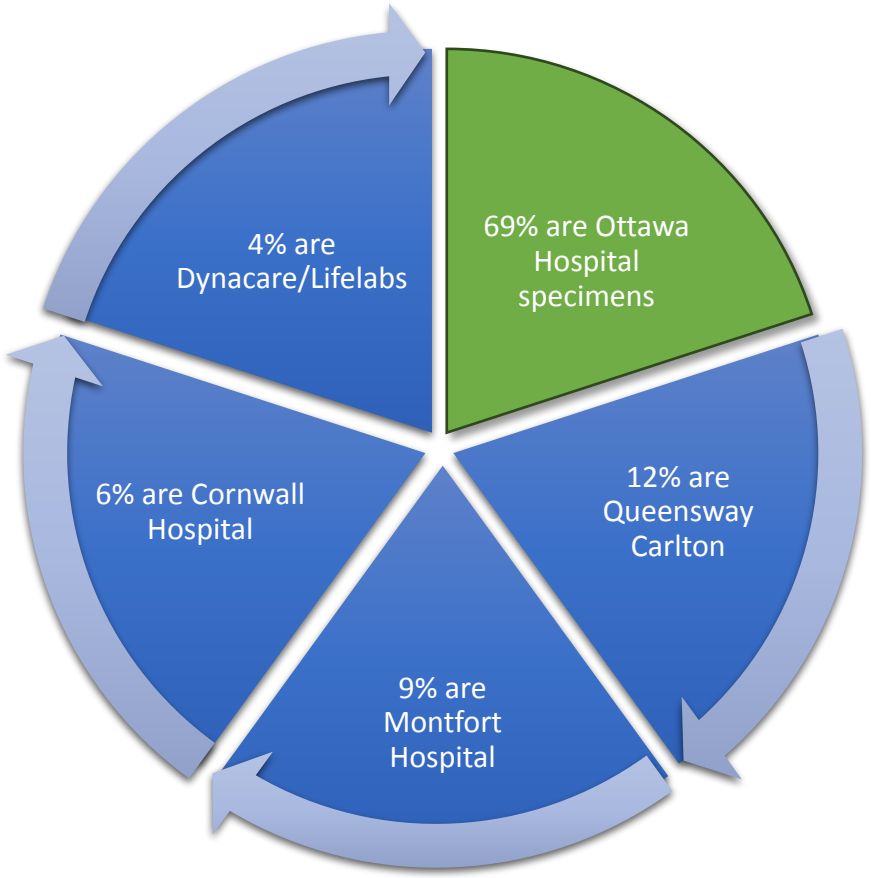


The order to block TAT is within 2 days (majority of cases - 72%) → Most of these are orders by pathologists

What about the longer TATs? → Most of these are orders by oncologists

Delays Before NGS:

Test ordering → Pathology review → Block received in lab



- Assume that **TATs <2 days** are due to pathology **reflex*** testing
- Assume that **TATs >2** days are **orders from clinicians** that require pathology review
- Depending on the site the **%TATs >2days is 15% to 39%**
- The **average TATs** range from **6-11 days**

***What is reflex testing?** A strategy in which testing for clinically actionable molecular targets is ordered by the pathologist at the time of diagnosis. **Why?** May be beneficial for expediting treatment decisions

Some final words:

Can the order-block TAT be reduced?

Process improvements needed:
Will require streamlining the process for requesting blocks/slides/pathology review

Regional Centralization Rocks:
A single pathology LIS for EORLA member hospitals does reduce the time required to locate the original diagnostic reports and confirm specimen IDs

Paper & Faxing is here to stay!
However, this pathology LIS does not eliminate the need for completing paper forms/faxing the requests

Opportunity to improve community TAT?
Preliminary analysis suggests that requests for specimens outside of EORLA member hospitals take on average 3-4 additional days

Delayed TAT: A Medical Oncology Perspective (10:05-10:20 a.m.)

Review:

- medical impact of delayed TAT
- clinical benefits of timely somatic testing in cancer
- importance of equal and timely access to CGP

Dr. Michael Raphael, Medical Oncologist, Odette Cancer Centre, Sunnybrook Health Sciences Centre

The impact of delayed turn-around time for molecular testing:
medical oncology perspective

Michael Raphael, MD, FRCPC
GI Medical Oncologist, Odette Cancer Centre

Sunnybrook
Odette Cancer Centre
when it matters MOST

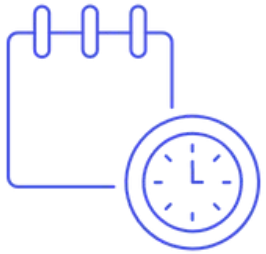
Disclosures

- No financial conflicts of interest

TAKE AWAY POINT #1

Delays in oncology can be deadly.

Delays to adjuvant chemotherapy for colorectal cancer



- Risk of death increased by **14%** for every 4 weeks of delay to start of chemotherapy (HR, 1.14; 95% CI, 1.10-1.17)

Biagi, Raphael, et al. JAMA 2011

Applying these results to an individual patient

- 65 year old male
- Good general health
- Stage 3 colon cancer (T3N2)

Timely initiation of treatment

- 5-year overall survival = 60%

4 week delay

- 5-year overall survival = 54%

(-) 6%

8 week delay

- 5 year overall survival = 48%

(-) 12%

Raphael, Biagi et al. JAMA 2011

TAKE AWAY POINT #1

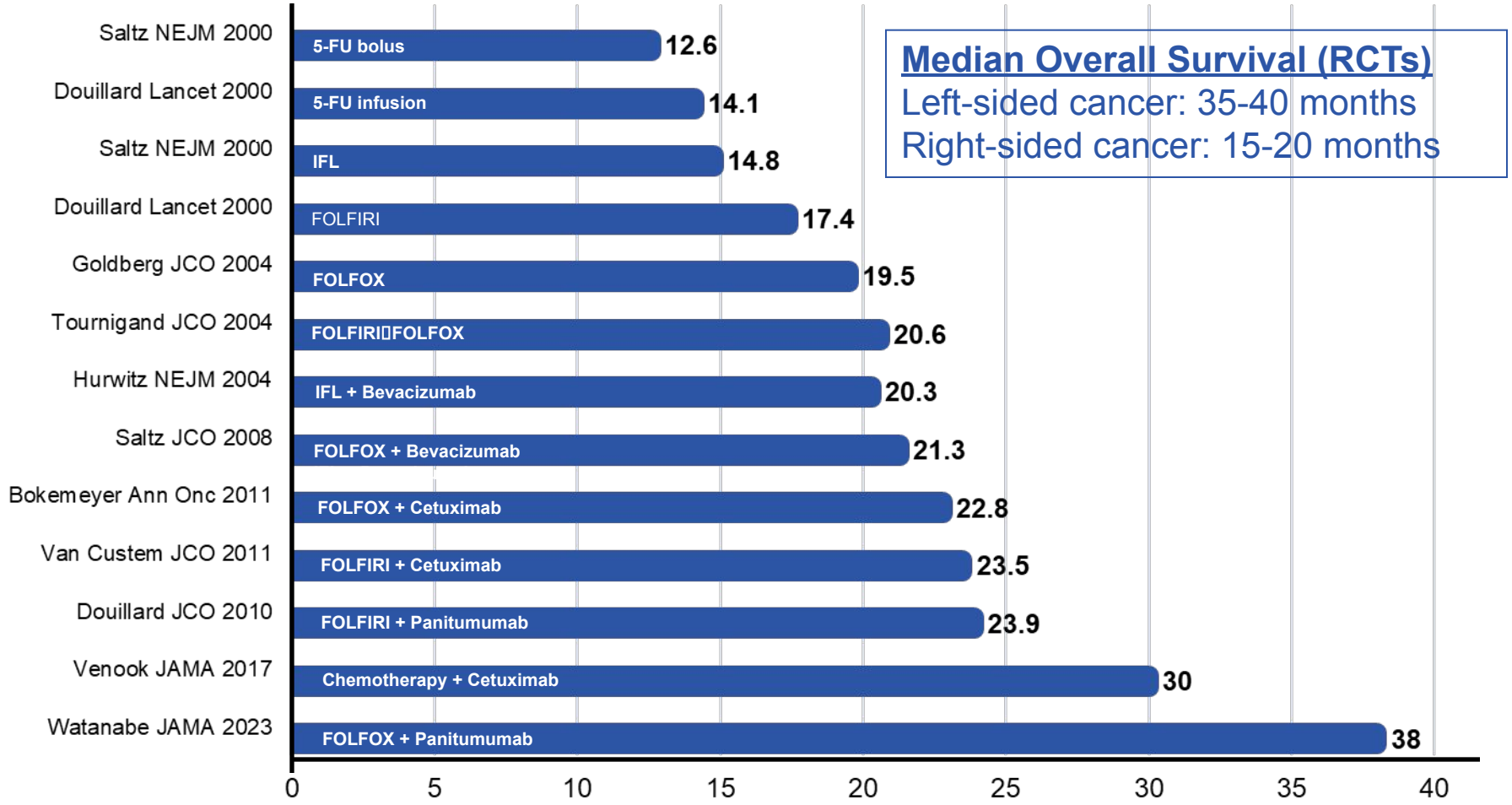
Delays in oncology can be deadly.

TAKE AWAY POINT #2

Our treatments are, slowly but surely, getting better

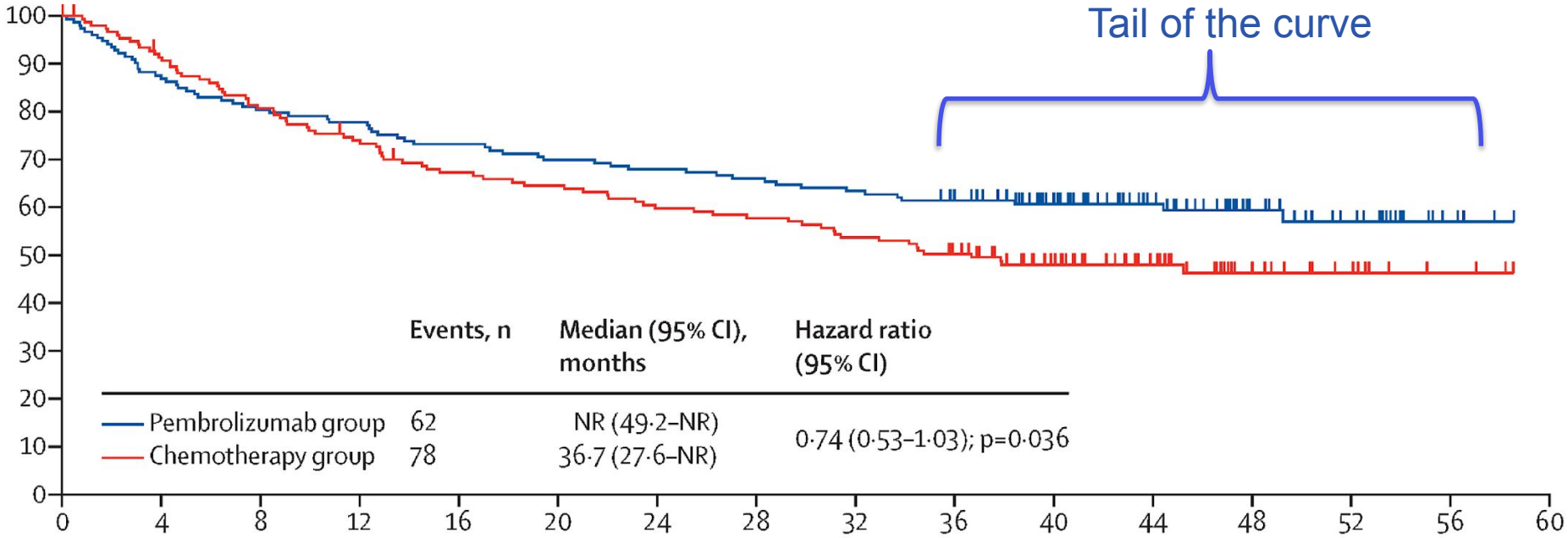
Metastatic Colorectal Cancer

A steady march towards improved overall survival



Median Overall Survival (RCTs)
Left-sided cancer: 35-40 months
Right-sided cancer: 15-20 months

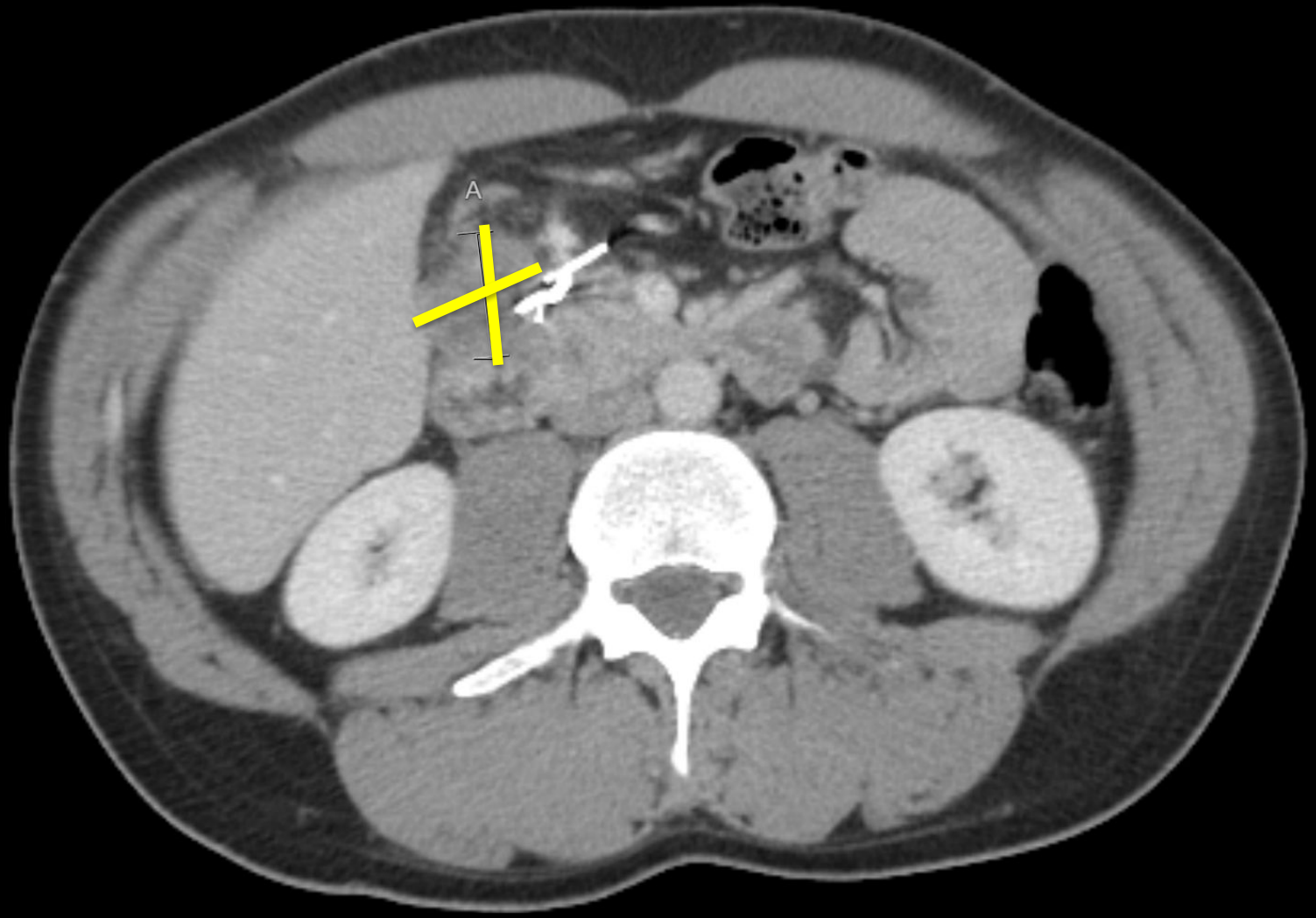
Metastatic Colorectal Cancer
Cured



Diaz Jr et al. Lancet Oncol 2022

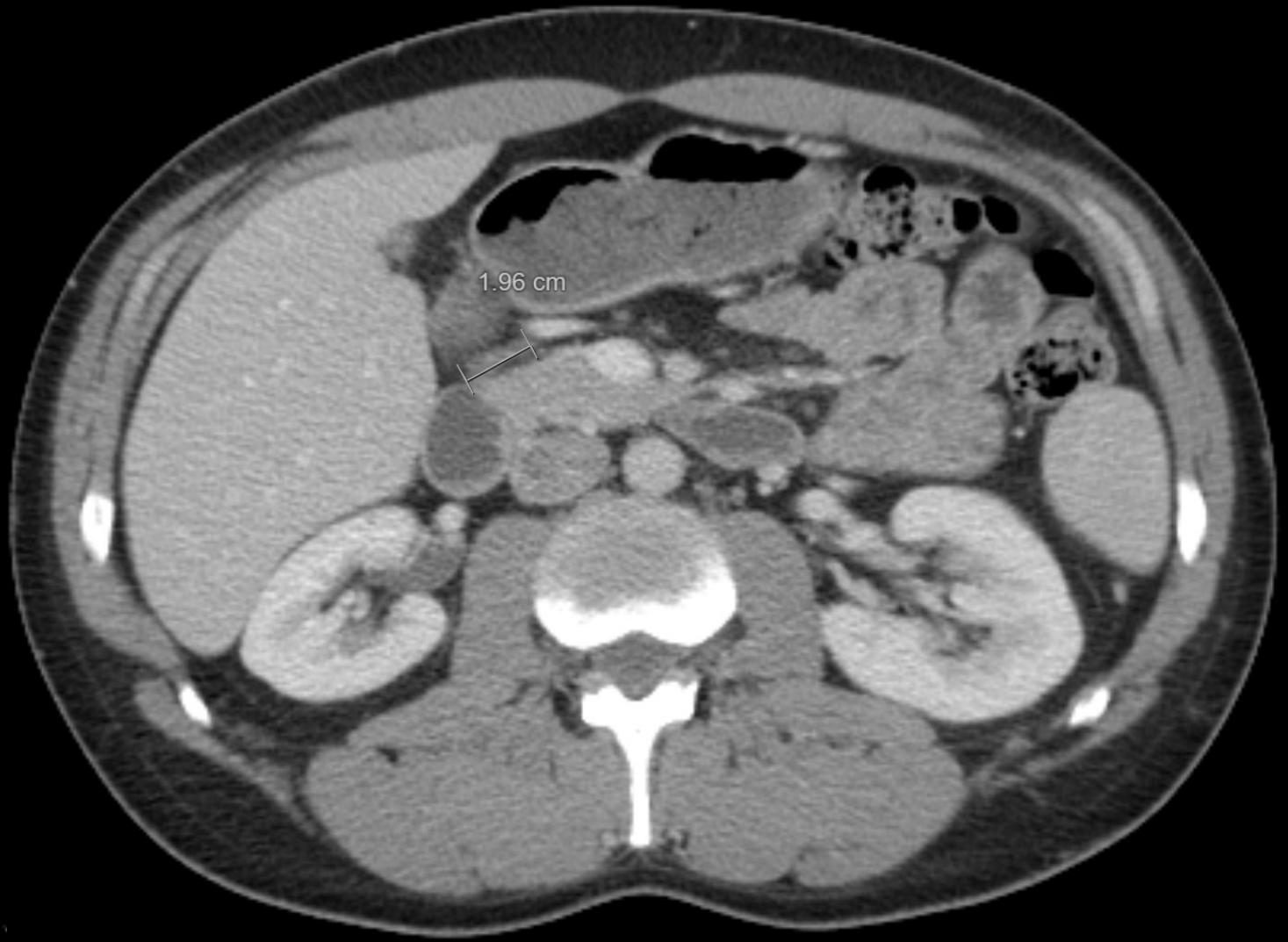
Sunnybrook
Odette Cancer Centre

June 2020



33 Male. Metastatic MSI-H Colorectal Cancer

July 2024



Off all treatment since June 2022

TAKE AWAY POINT #2

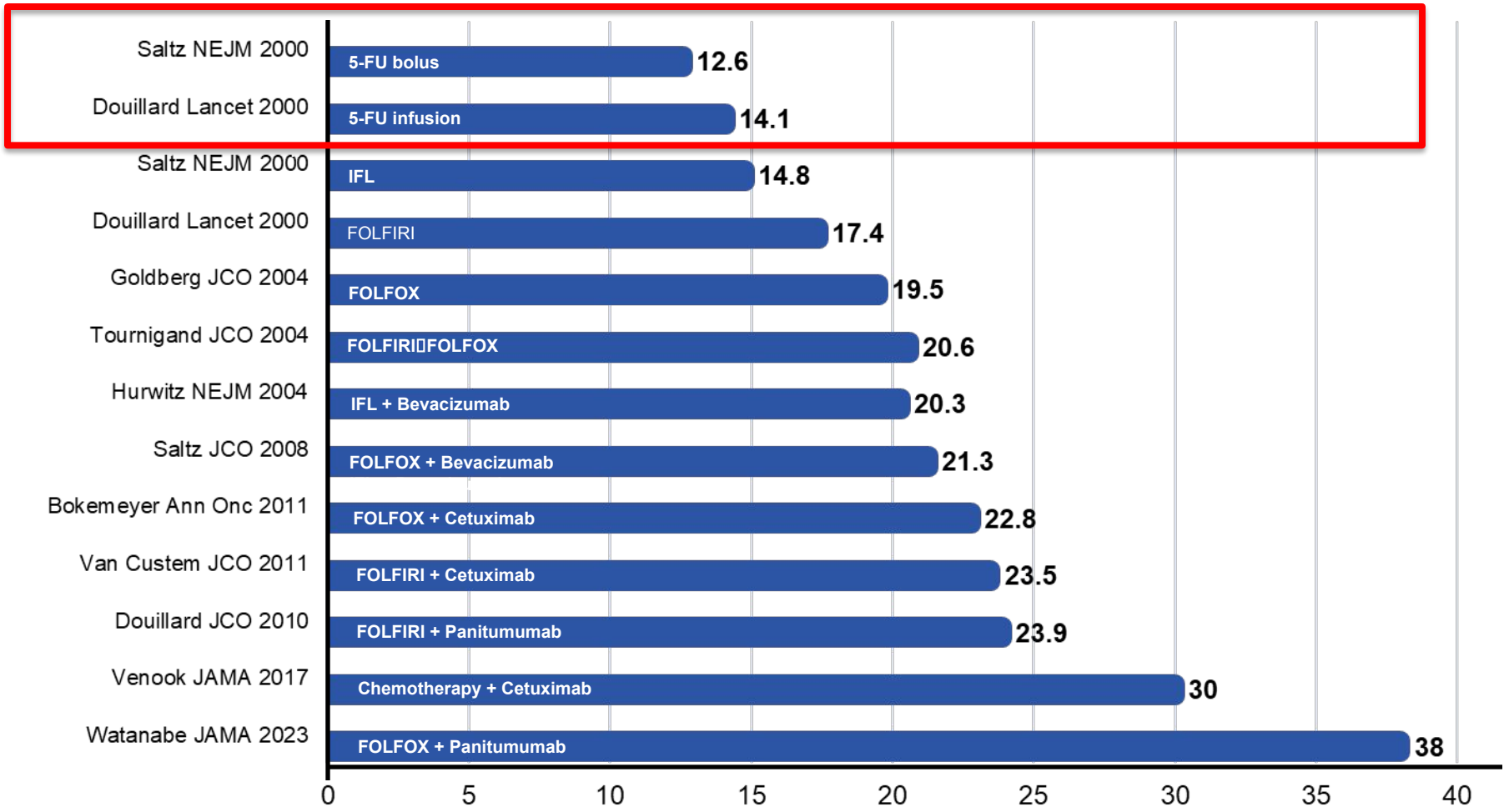
Our treatments are, slowly but surely, getting better

TAKE AWAY POINT #3

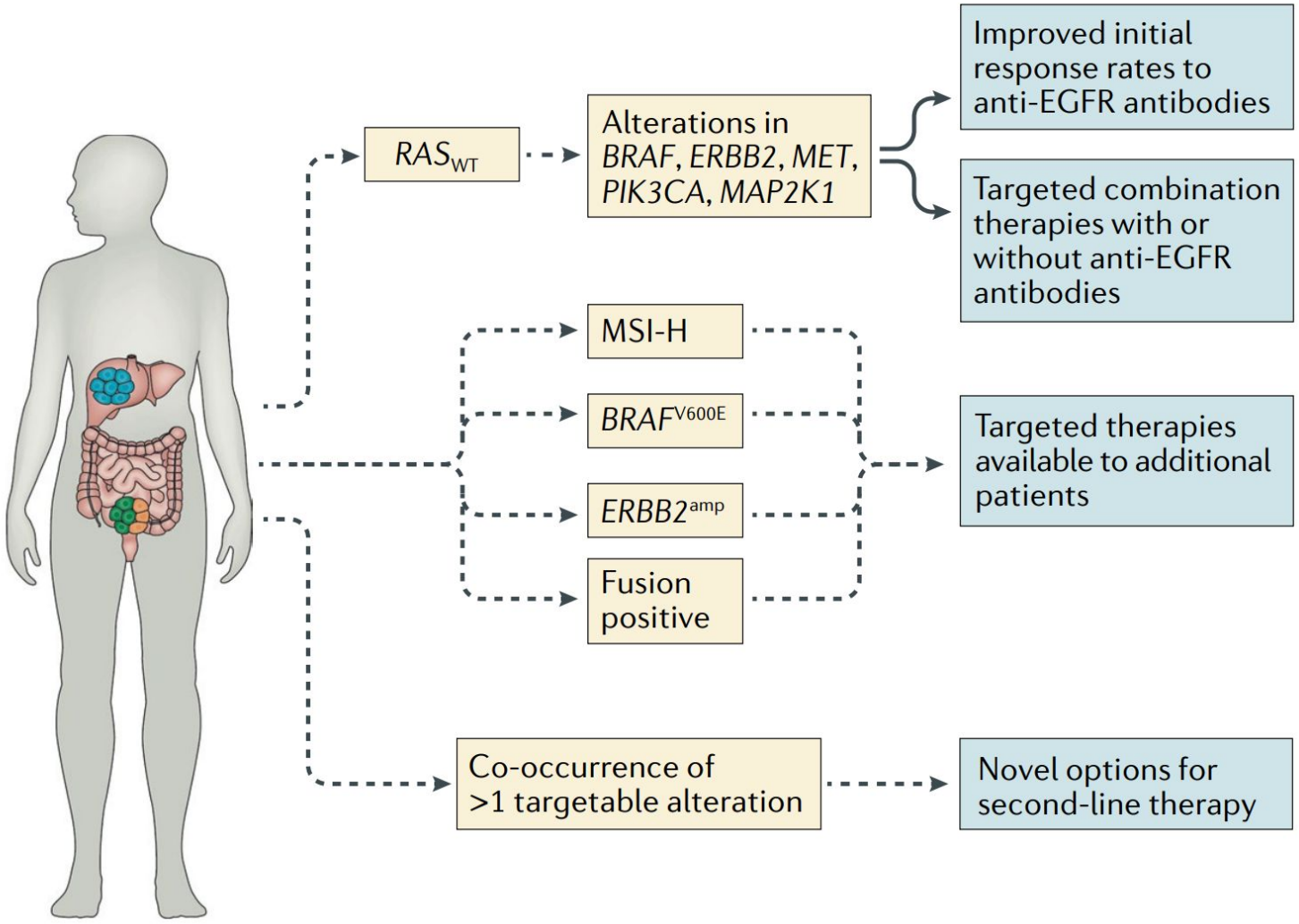
To select the right treatment, we need biomarkers, and we need them quickly

Metastatic Colorectal Cancer

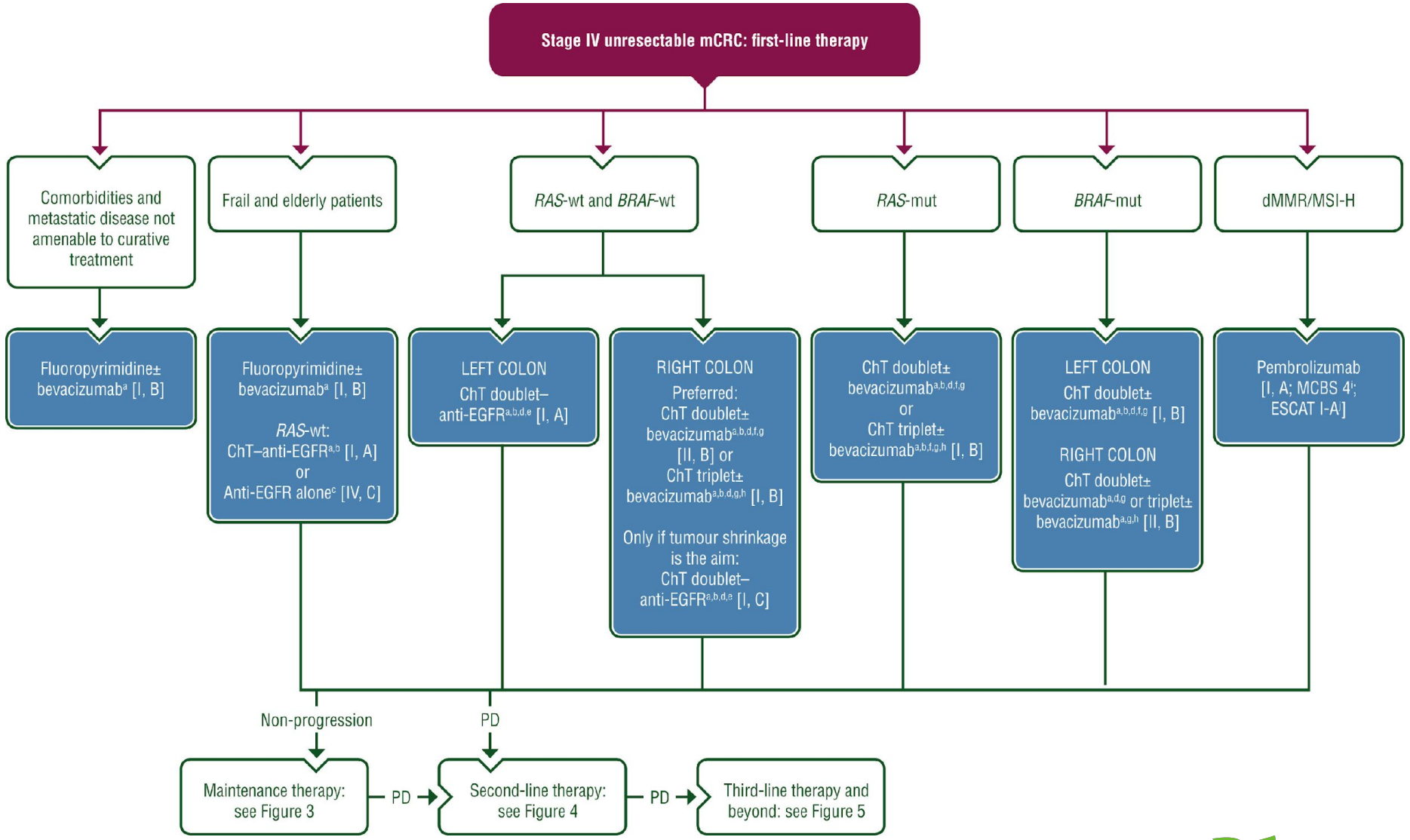
A steady march towards improved overall survival



Median Overall Survival (Months)



Sveen et al. NRCO 2019



Cervantes et al. Ann Oncol 2023

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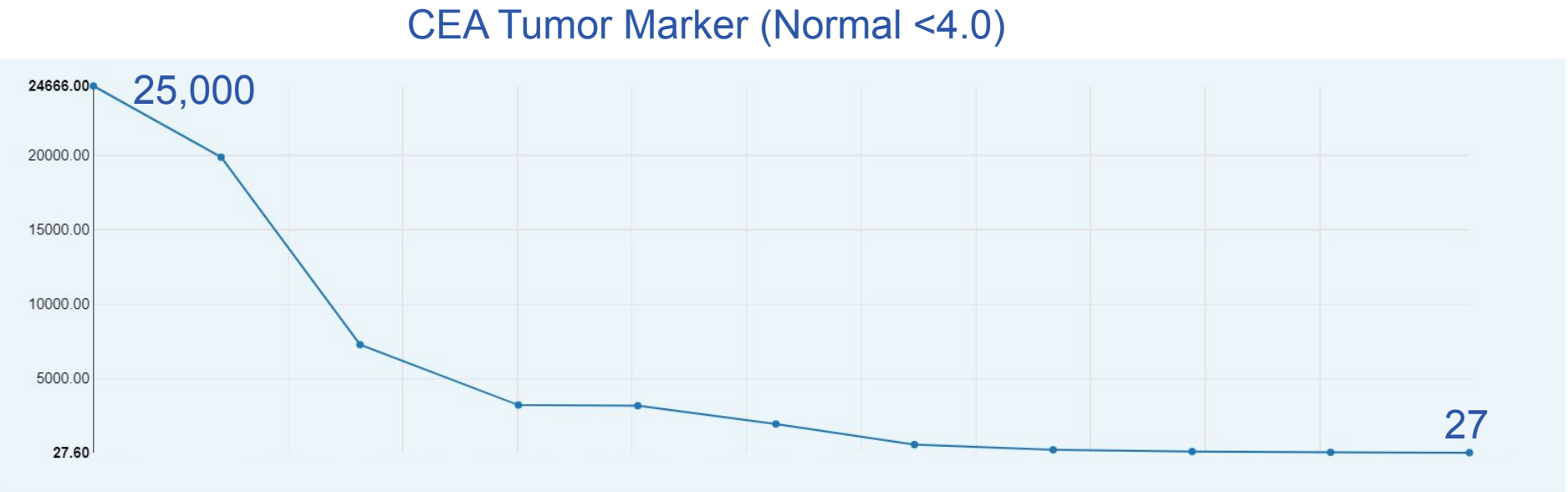
25 year old with metastatic colorectal cancer

In house NGS: eRAS wild-type
Treatment: FOLFOX + Panitumumab



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TAKE AWAY POINT #3

To select the right treatment, we need biomarkers

TAKE AWAY POINT #4

We need our biomarker data ASAP, so we can start caring for our patients ASAP

Imagine a loved one in their first meeting with their oncologist.

- **They are told devastating news**:
  - They have a metastatic cancer

- **The are told even more devastating news:**
  - There are treatments available to help control the cancer and manage symptoms, but there is no cure. They will die from this cancer

- **The important questions start racing through their minds:**
  - What is the treatment?
  - What is the prognosis?

Imagine having to tell this patient and their family that you cannot answer these life-altering questions because you don't yet have all their result back

TAKE AWAY POINT #4

We need our biomarker data ASAP, so we can start caring for our patients ASAP

Panel Discussion (10:20 – 10:30 a.m.)

THANK YOU!

QUESTIONS?

COMMENTS?

What's Up With Turn-Around-Time (TAT)?

Tackling Cancer Genomic Testing Inequities in Ontario

THANK YOU