
THE UNIVERSITY of ADELAIDE
CANCER TREATMENT TOXICITIES GROUP
Integrating the pathogenesis, prediction and prevention of cancer related side effects
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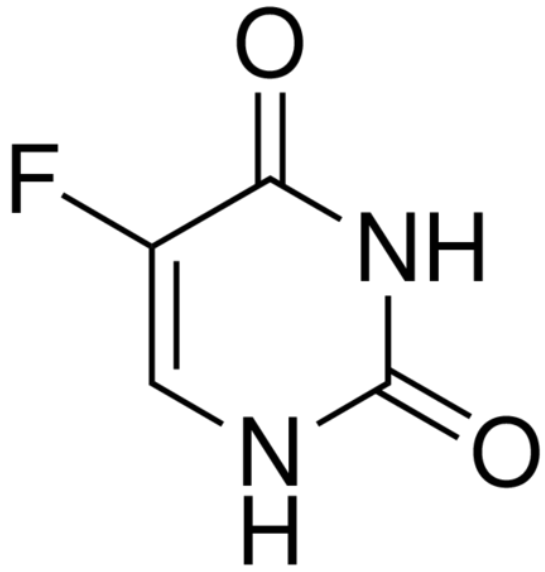
Personalized Supportive Care for Patients Receiving 5-FU:
Interim analysis of multivariate SNP risk prediction for severe GI toxicity
seek LIGHT

Faculty Disclosure

x	No, nothing to disclose
	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*

5-Fluorouracil (5-FU) induces GI Toxicity



- 5-FU = Antimetabolite that inhibits thymidylate synthase[1]
- Breast, upper GI and colorectal solid tumors[1]
- 20 - 40% of patients experience toxicity[2]
- Severe toxicity (grade ≥ 3[5]);
  - Treatment delays and dose reductions[2]
  - 2° consequences (pain, dehydration)[2]
  - financial burden[3]
  - ↓ quality of life[4]

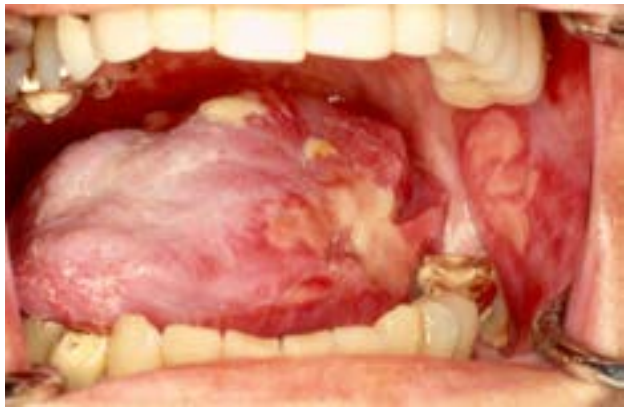
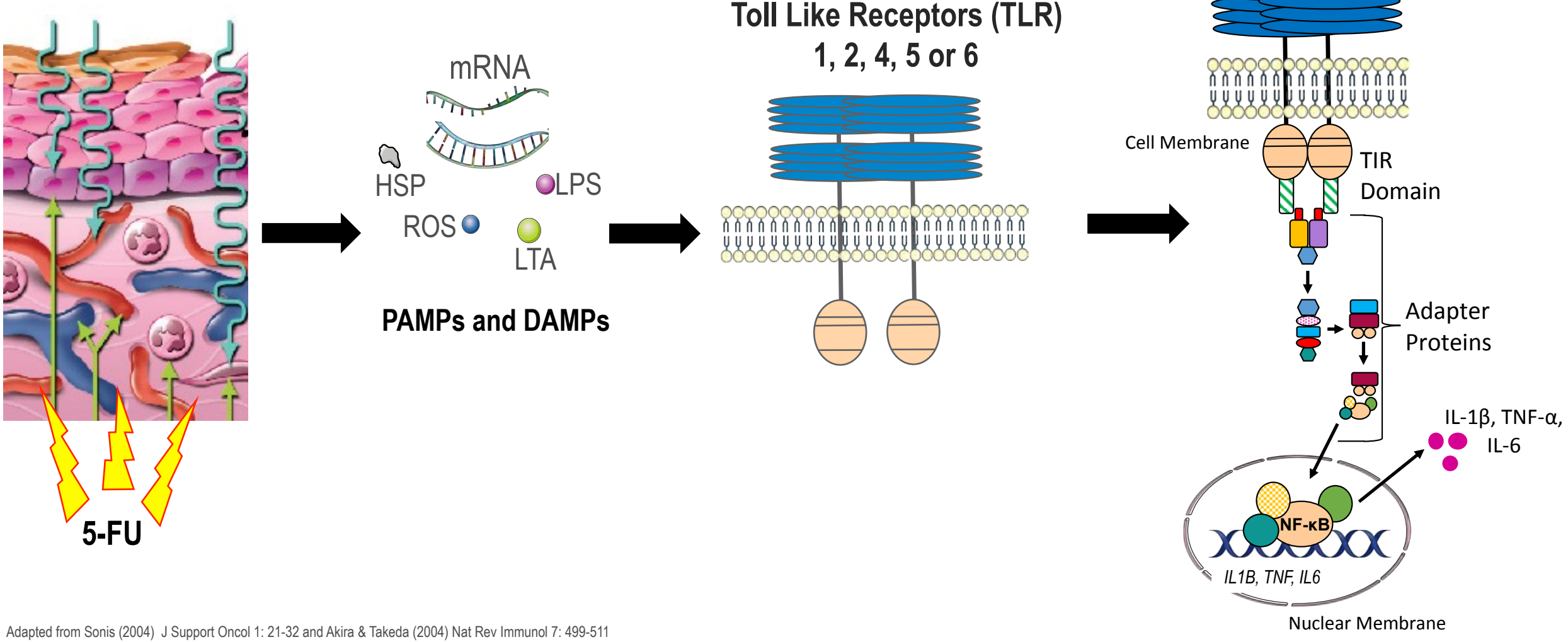


Image from Prof Richard Logan

1. Thorn et al (2011) Pharmacogenet Genomics 21: 237-234; 2. Sonis (2004) Nat Rev Cancer 4: 277-284; 3. Carlotto et al (2013) Pharmacoeconomics 31: 753-766; 4. Keefe et al (1997) Clin Sci 92: 385-389; 5. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

Pathophysiology of GI toxicity



Adapted from Sonis (2004) J Support Oncol 1: 21-32 and Akira & Takeda (2004) Nat Rev Immunol 7: 499-511

The Problem

- **Q: Why does 'Patient B' suffer GI toxicity and not 'Patient A'?**

  A: ????

We need a predictor for severe GI toxicity risk

- Personalization of supportive care to reduce GI toxicity severity

'Patient A'

Demographics

Mid 40's | Female | Healthy BMI
Non-smokers | No medical history

Diagnosis

Left Breast Cancer
Grade 3 | 5-FU-based regimen

'Patient B'

Chemotherapy side effects

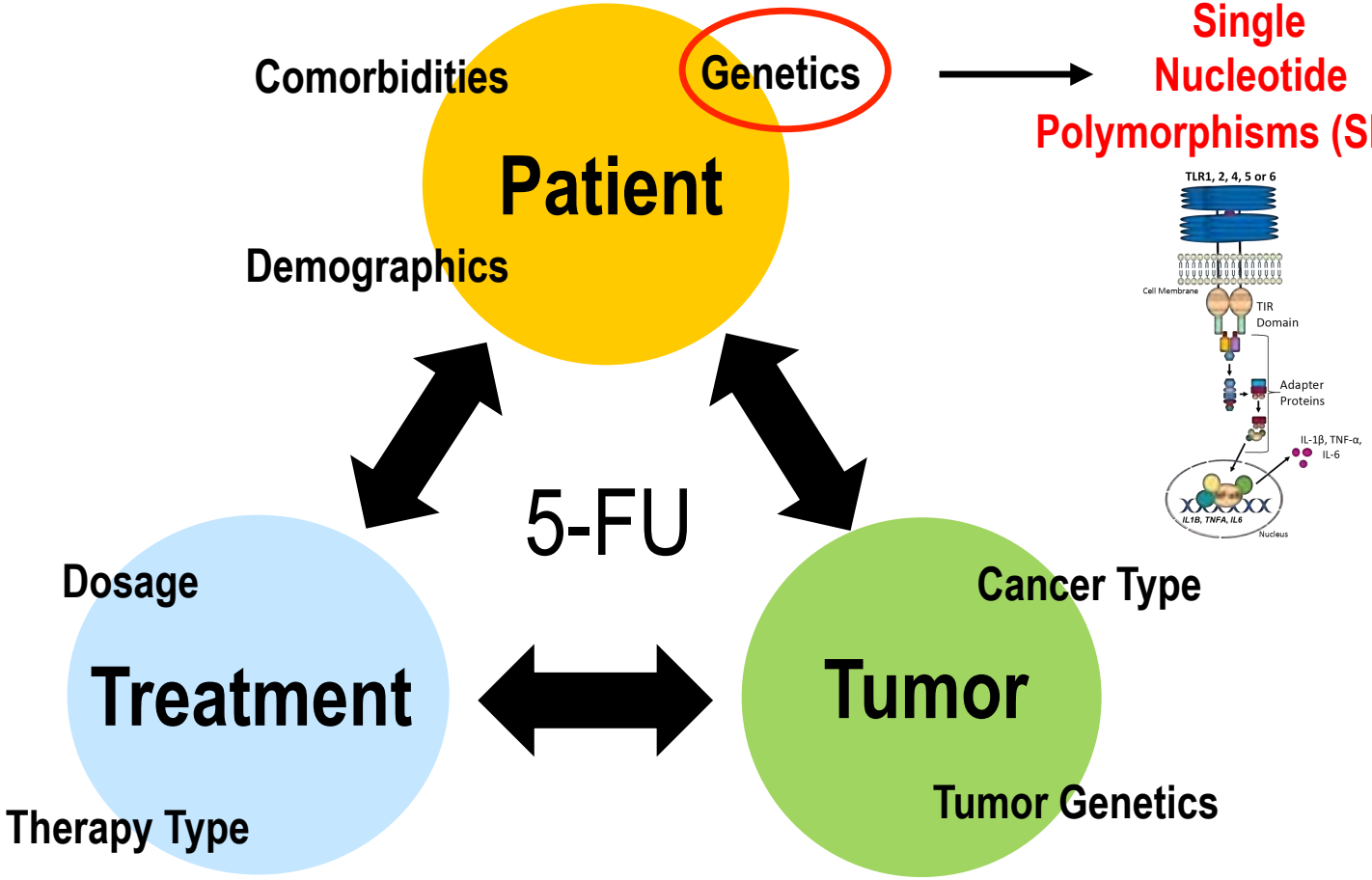
- Fatigue
- Grade 1 nausea

Chemotherapy side effects

- Fatigue
- **Grade 3 diarrhea**
- **Grade 2 mucositis**

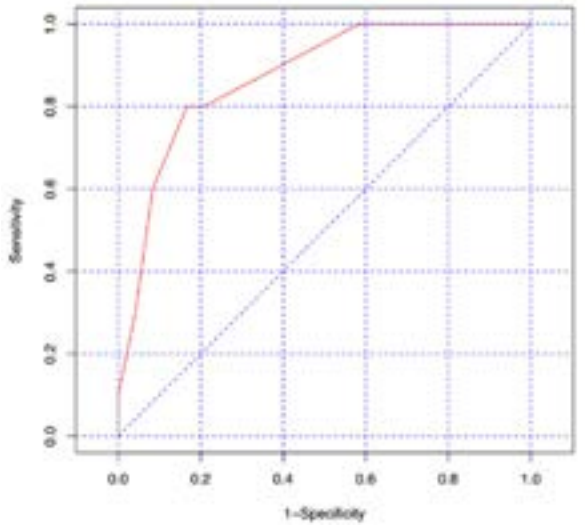
Hospitalisation

The Story So Far..



Single Nucleotide Polymorphisms (SNPs)

Salivary Predictors in Treatment (SPiT) Study



In 34 patients, severe GI toxicity risk model[1]

- *TLR2* and *TNF*
- Colorectal and gastric cancer types
- ROC AUC 87%

1. Coller *et al* (2015) *Supp Care Cancer* 23: 1233-1236

SPiT Validation (SPiT-V) Study

Pilot study → Validation!!

Aim: To investigate the association between SNPs of the TIR domain innate immune signaling pathway and severe GI toxicity following 5-FU-based treatment

Methods

- Retrospective study; multi-site state-wide
- 5-FU-based therapy
- Clinical case notes = demographics, treatment and toxicity data
- Genomic DNA = genotype analysis[1]

1. Coller *et al* (2015) *Supp Care Cancer* 23: 1233-1236

SPiT-V Study – Participant Demographics

- n = 114
- Two toxicity groups:
  - No/mild (≤ 2)[1]
  - Severe (≥ 3, treatment cessation or reduction)[1]
- Cancer type and treatment protocol significant (P < 0.02)

	No/mild (n = 90)	Severe (n = 24)	P Value
Sex (n (%))			
Female	63 (71%)	11 (46%)	0.03
Male	27 (29%)	13 (54%)	
Cancer Type (n (%))			
Breast	55 (62%)	5 (21%)	0.001*
Colorectal	32 (35%)	16 (66%)	
Upper GI	3 (3%)	3 (13%)	
Hospital (n (%))			
Royal Adelaide Hospital	31 (35%)	7 (29%)	0.81
Flinders Medical Centre	59 (65%)	17 (71%)	
Treatment Protocol (n (%))			
5-FU monotherapy	10 (11%)	10 (42%)	<0.0001**
5-FU in combination	73 (82%)	6 (25%)	
Capecitabine	7 (7%)	8 (33%)	
Age			
Median (range)	61 (32 – 86)	68 (28 – 78)	0.03

1. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

SPiT-V Study – Building the Predictive Risk Model

Covariates

- Sex
- Age
- Hospital
- Cancer type
- Treatment protocol
- Number of treatment cycles

SNPs

IL1B, *IL12*, *IL6*, *TNF*, *IL10*, *TGF*, *ICE (CASP1)*, *IL6R*, *TLR2*, *TLR4*, *MD2*, *MYD88*, *BDNF*, *CRP*

→ **Each predictor is added individually to the model**

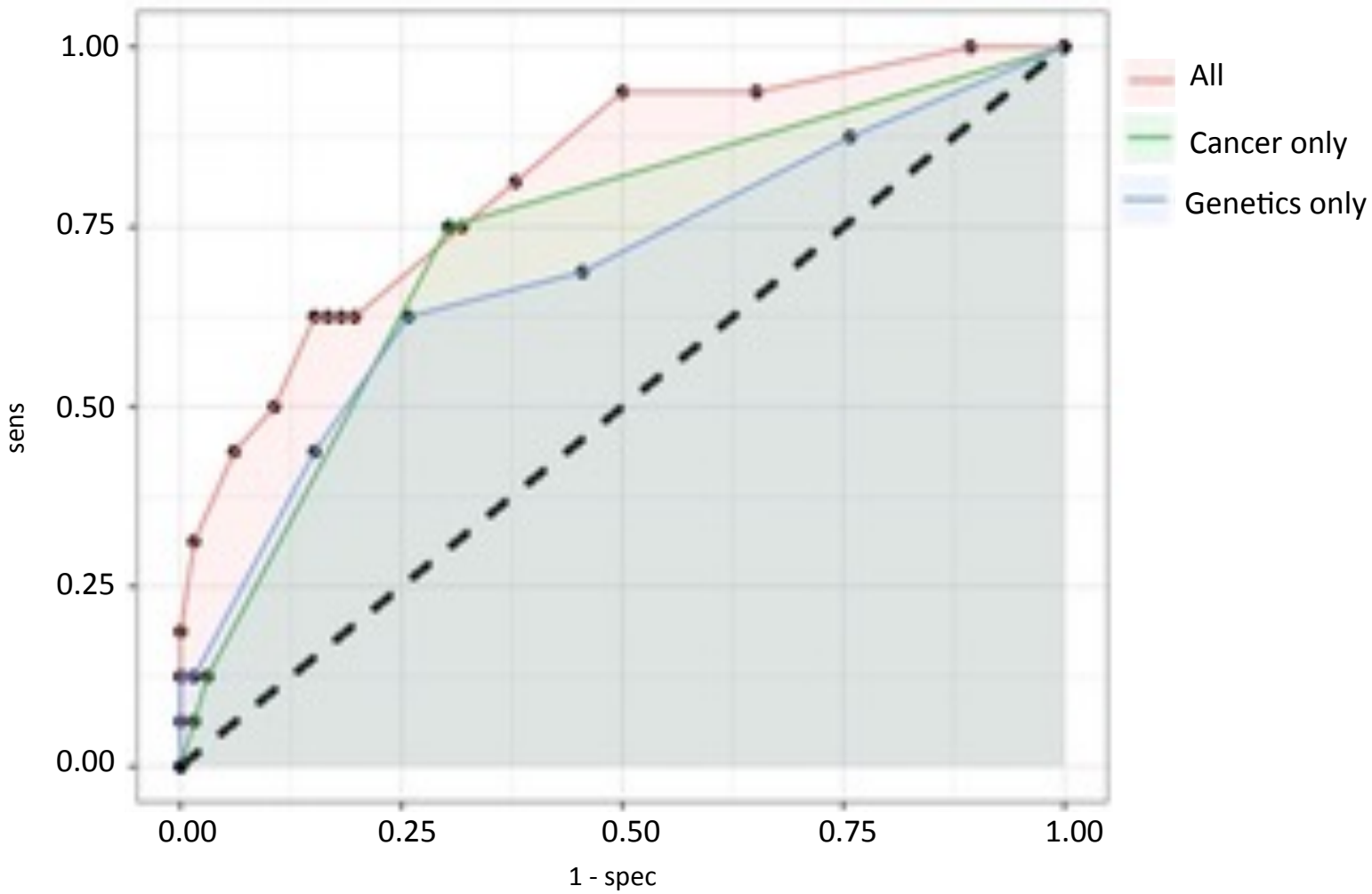
→ Improves model (ANOVA) → ✓

→ Does not improve model (ANOVA) → ✗

SPiT-V Study – Interim Predictive Risk Model

Predictive severe GI toxicity risk model

- n = 105
- *IL1B* rs16944 and rs1143634
- Colorectal and gastric cancer types
- ROC AUC 82%



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