Cancer screening post renal transplant- how far and how long?

Presented by
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DOES

?

Overview

- Cancer epidemiology in kidney transplantation
- Population-based cancer screening programs
- Guiding principles of cancer screening in the general population
- Recommendations for cancer screening in transplant recipients
- Examples of cancer screening in transplant recipients
- Patient preferences on cancer screening
- Clinician's perspectives on cancer screening

Cancer is common after kidney transplantation

Table 1 | **Standardized incidence ratios from registry and multicentre studies for various cancers**

Region (years; number of patients)	Standardized incidence ratios (95% CI)											Refs
	All cancers	Breast cancer	Cervical cancer	Colorectal cancer	Kidney cancer	Lip cancer	Lung cancer	Malignant melanoma	NHL	NMSC	Prostate cancer	
Canada[a] (1981–1998; 11,391)	2.5 (2.3–2.7)	1.3 (1.0–1.7)[b]	1.6 (0.6–3.4)	1.4 (1.0–1.8)	7.3 (5.7–9.2)	31.3 (23.5–40.8)	2.1 (1.7–2.5)	1.9 (1.2–3.0)	8.8 (7.4–10.5)	NA	0.9 (0.6–1.3)	13
USA[c] (NS; 113,038)	NA	0.95 (0.86–1.0)	1.1 (0.8–1.5)	1.2 (1.1–1.3)	6.4 (5.9–6.8)	18 (15–22)	1.6 (1.1–1.3)	2.8 (2.5–3.2)	5.9 (5.5–6.3)	NA	0.92 (0.85–0.98)	15
Italy[d] (1997–2007; 7,217)	1.7 (1.6–1.9)[e]	0.8 (0.5–1.2)[b]	NA	0.8 (0.5–1.2)	4.9 (3.4–6.8)	9.4 (3.1–22.0)	1.1 (0.8–1.6)	1.8 (0.9–3.3)	4.5 (3.2–6.1)	NA	1.7 (1.2–2.3)	9
Italy[f] (1980–2011; 3,537)	1.5 (1.3–1.8)[g]	1.2 (0.8–1.8)	8.9 (4.4–17.7)	1.2 (0.7–1.9)[h]	7.0 (5.0–9.8)	NA	1.1 (0.1–1.7)	1.0 (0.4–3.0)	7.9 (6.0–10.5)	29.3 (26.0–33.1)	1.3 (0.8–2.1)	11
Sweden[i] (1970–2008; 7,952)	6.5 (6.3–6.8)	1.2 (0.9–1.8)	2.4 (1.2–4.4)	2.3 (1.8–2.9)[h]	6.2 (4.8–7.9)	46 (35–59)	1.7 (1.3–2.2)	2.3 (1.7–3.1)	4.8 (3.8–5.9)	121 (116–127)[j]	1.1 (0.9–1.3)	6
UK[k] (1980–2007; 25,104)	2.4 (2.3–2.5)[e]	1.0 (0.8–1.2)	2.3 (1.4–3.5)	1.8 (1.6–2.1)	7.9 (6.7–9.3)	65.5 (49.9–84.6)	1.4 (1.2–1.6)	2.6 (2.0–3.3)	12.5 (11.2–13.8)	16.6 (15.9–17.3)	1.1 (0.9–1.4)	4
Australia and New Zealand[l] (1982–2003; 10,180)	3.3 (3.1–3.5)	1.0 (0.8–1.3)	2.5 (1.3–4.3)	2.4 (1.9–2.9)[h]	5.0 (3.4–7.1)	47.1 (41.8–52.9)	2.5 (2.0–3.0)	2.5 (2.1–3.1)	9.9 (8.4–11.5)	NA	1.0 (0.7–1.3)	10,12
Hong Kong[m] (1972–2011; 4,674)	2.9 (2.6–3.3)	1.7 (1.0–2.8)[b]	7.2 (3.9–13.4)	1.8 (1.2–2.5)	12.5 (8.5–18.4)	NA	1.7 (1.2–2.4)	9.1 (2.3–36.3)	15.8 (11.9–21.0)	7.4 (4.9–11.2)	0.8 (0.4–2.0)	3
Taiwan[n] (1997–2008; 4,716)	3.8 (3.4–4.2)	1.1 (0.6–1.9)[b]	0.88 (0.22–3.0)	2.0 (1.1–3.5)[h]	44.3 (36.2–54.1)	NA	4.8 (2.7–8.5)	5.4 (0.8–38.2)	4.8 (2.6–8.9)[o]	2.3 (0.9–6.1)	1.8 (0.7–4.8)	8

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Cancer in kidney transplant recipients

*Eric Au[1], Germaine Wong[1,2] and Jeremy R. Chapman[1]**

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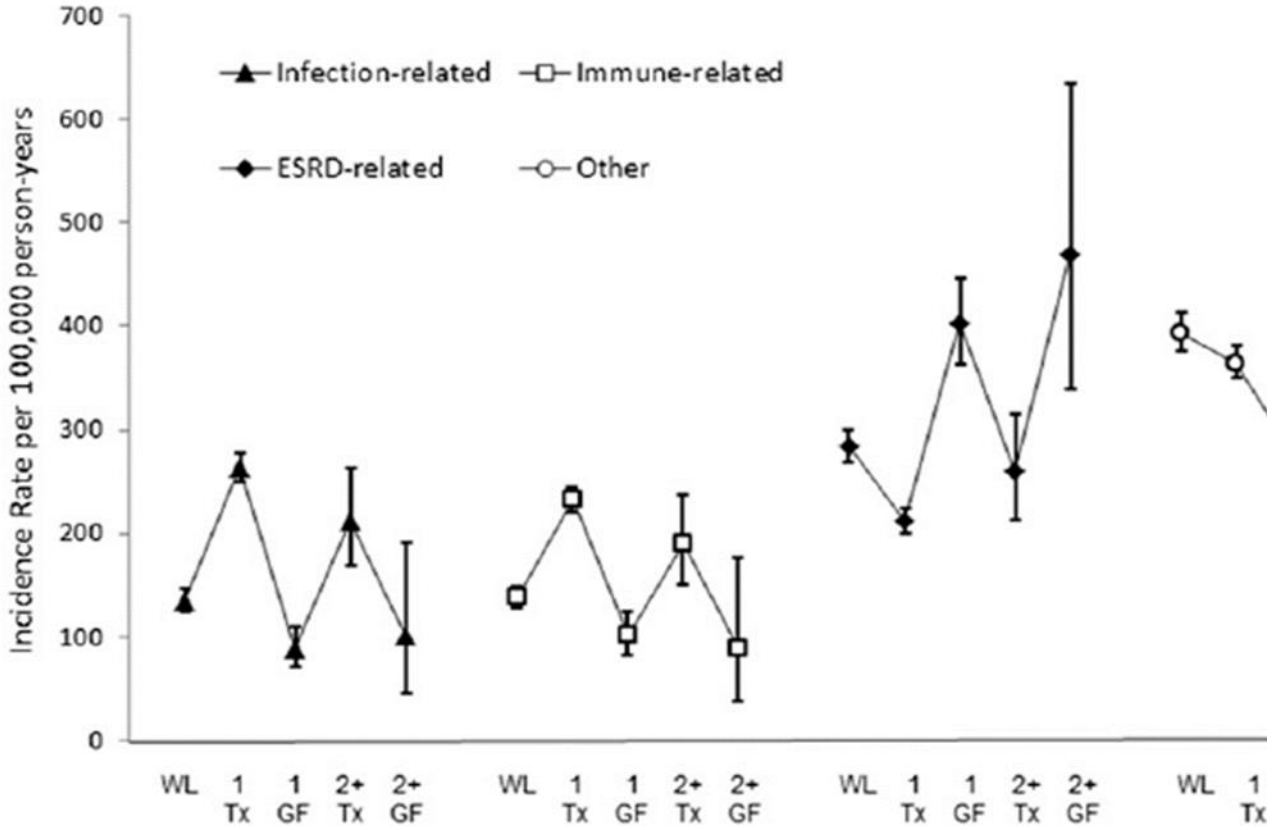
Variation in cancer incidence in patients with ESKD during kidney function and non-function

Table 3. Standardized incidence ratios across intervals of kidney function and nonfunction

Cancer Type	Standardized Incidence Ratio (95% CI), by Interval				
	Waitlist	First Transplant	First Graft Failure	Second or Higher Transplant	Second or Higher Graft Failure
Infection-related					
Kaposi sarcoma	6.4 (2.8 to 13)	55 (44 to 68)	5.9 (0.15 to 33)	33 (4 to 120)	100 (2.5 to 560)
Non-Hodgkin's lymphoma	1.7 (1.5 to 2)	5.9 (5.5 to 6.3)	1.3 (0.84 to 2)	5.8 (4.1 to 7.8)	0 (0 to 2.7)
Hodgkin's lymphoma	0.87 (0.45 to 1.5)	3.4 (2.6 to 4.3)	0.71 (0.09 to 2.6)	3.1 (0.86 to 8.1)	3.3 (0.08 to 19)
Liver	1.8 (1.5 to 2.2)	1 (0.79 to 1.3)	0.99 (0.45 to 1.9)	0.64 (0.08 to 2.3)	1.6 (0.04 to 9.1)
Stomach	1.4 (1.1 to 1.7)	1.6 (1.3 to 1.9)	1.5 (0.84 to 2.6)	1.4 (0.37 to 3.5)	0 (0 to 6.7)
Oropharynx[a]	1.2 (0.88 to 1.7)	1.3 (0.97 to 1.7)	0.78 (0.21 to 2.0)	1.9 (0.52 to 4.9)	0 (0 to 9.5)
Anus	2.6 (1.7 to 3.8)	4.8 (3.7 to 6.2)	3 (0.96 to 6.9)	10 (4.1 to 21)	0 (0 to 28)
Cervix	0.89 (0.59 to 1.3)	1.1 (0.75 to 1.5)	0.71 (0.19 to 1.8)	1.8 (0.48 to 4.6)	2.3 (0.06 to 13)
Other genital[b]	3 (2 to 4.2)	5.1 (4 to 6.5)	6.8 (3.4 to 12)	18 (8.9 to 32)	36 (9.9 to 93)
Immune-related					
Lung	1.2 (1.1 to 1.3)	1.6 (1.5 to 1.7)	1.3 (1 to 1.6)	2.1 (1.5 to 2.9)	1.4 (0.47 to 3.3)
Melanoma	1.5 (1.2 to 1.8)	2.8 (2.5 to 3.2)	0.83 (0.38 to 1.6)	2.4 (1.3 to 4)	0.98 (0.03 to 5.5)
Lip	3.5 (1.7 to 6.2)	18 (15 to 22)	4.3 (0.53 to 16)	24 (7.7 to 56)	50 (6.1 to 180)
Nonepithelial skin[c]	2.5 (1.5 to 3.9)	13 (11 to 15)	5.5 (2.2 to 11)	25 (14 to 44)	0 (0 to 37)
ESRD-related					
Kidney	9 (8.4 to 9.6)	6.4 (5.9 to 6.8)	18 (16 to 20)	13 (10 to 16)	28 (19 to 39)
Urinary tract	1.6 (1.3 to 1.9)	1.9 (1.6 to 2.2)	1.8 (1.1 to 2.8)	3 (1.6 to 5.3)	7.5 (2.4 to 17)
Thyroid	4 (3.5 to 4.6)	2.9 (2.5 to 3.4)	7.4 (5.8 to 9.4)	2.1 (1 to 3.8)	6.7 (2.4 to 15)
Other					
Colorectum	1.2 (1.1 to 1.3)	1.1 (0.96 to 1.2)	0.95 (0.69 to 1.3)	1 (0.57 to 1.6)	1 (0.21 to 3)
Prostate	0.85 (0.78 to 0.92)	0.92 (0.85 to 0.98)	0.65 (0.5 to 0.83)	0.95 (0.65 to 1.3)	1.3 (0.55 to 2.5)
Breast	1.2 (1 to 1.3)	0.95 (0.86 to 1.0)	1.1 (0.86 to 1.4)	0.76 (0.45 to 1.2)	2.4 (1.1 to 4.5)
Esophagus	0.96 (0.68 to 1.3)	1.3 (1 to 1.7)	2.2 (1.1 to 3.8)	0.53 (0.01 to 2.9)	2.9 (0.07 to 16)
Pancreas	1.1 (0.86 to 1.4)	1.5 (1.3 to 1.8)	0.98 (0.47 to 1.8)	1.7 (0.62 to 3.7)	0 (0 to 5.8)
Uterus	0.93 (0.72 to 1.2)	0.94 (0.75 to 1.2)	1.4 (0.77 to 2.3)	1.6 (0.64 to 3.3)	0 (0 to 5.8)
Myeloma	1.8 (1.5 to 2.2)	1.8 (1.4 to 2.1)	2.2 (1.3 to 3.6)	2.6 (0.97 to 5.7)	4.4 (0.54 to 16)
Leukemia	1.4 (1.1 to 1.8)	1.8 (1.5 to 2.1)	2.7 (1.7 to 4.1)	2.3 (1 to 4.6)	1.6 (0.04 to 9)

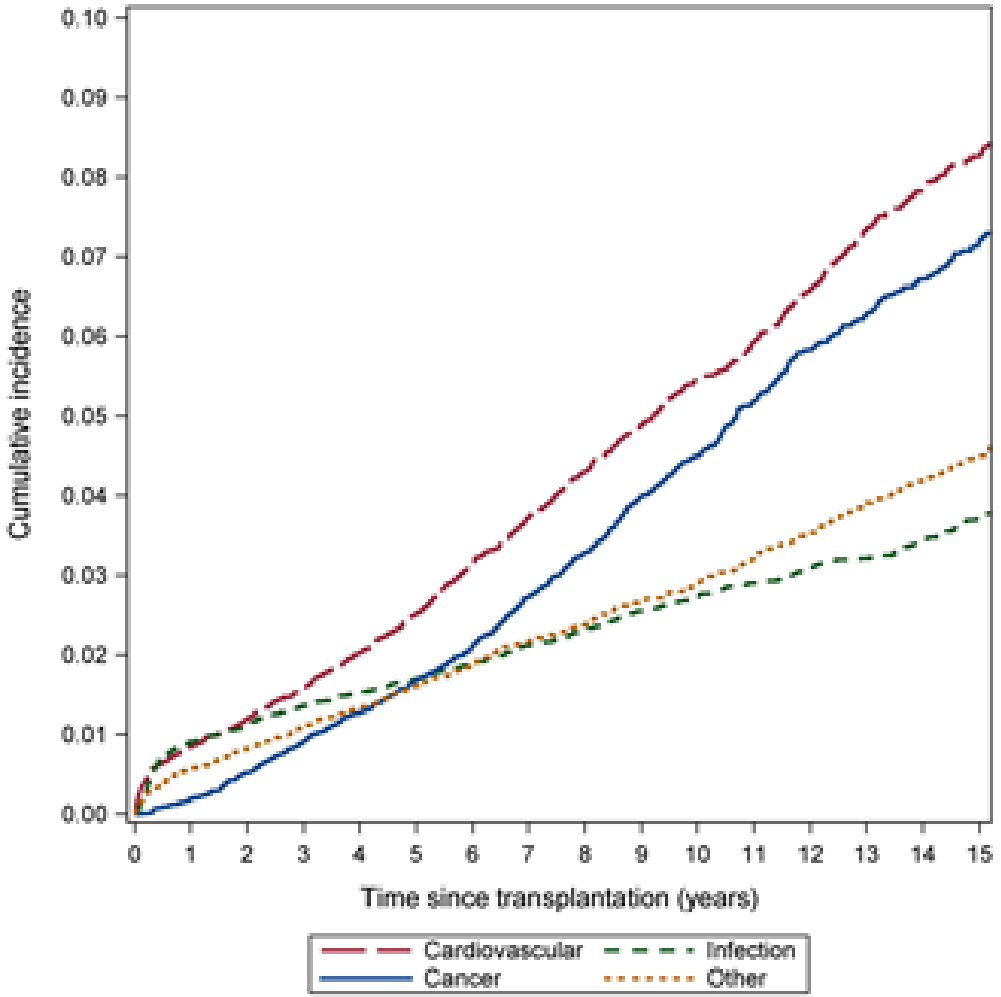
Yanik et al 2016 JASN

Variation in the incidence rate of "grouped" cancers



- 'See saw' pattern of cancer incidence during good graft function and graft failure for infection and immune related cancers
- 'Reverse see-saw' pattern of cancer incidence for ESKD related cancers

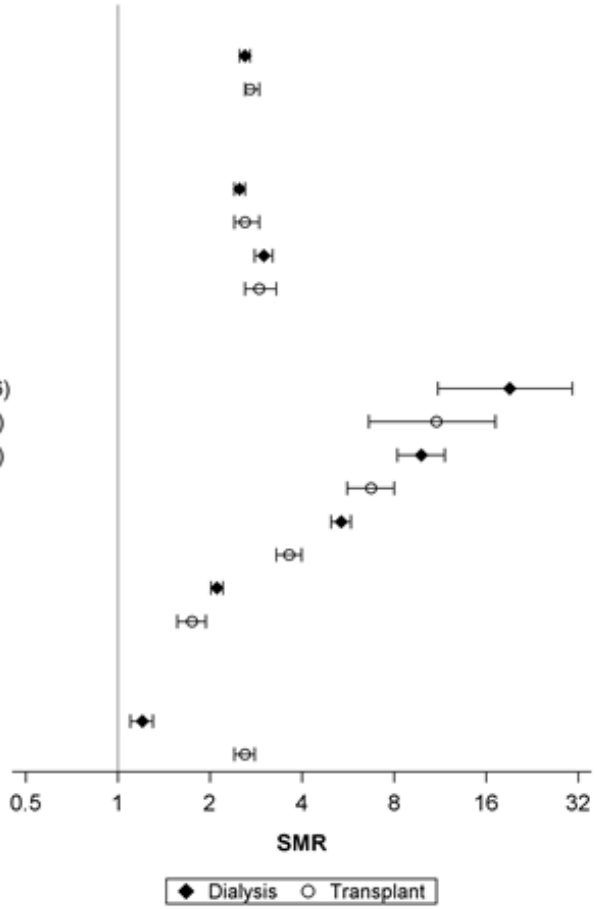
Cancer is also ‘deadly’ after kidney transplantation



After cardiovascular disease, cancer is the second most common cause of death in kidney transplant recipients

Absolute and relative risk of cancer death after kidney transplantation

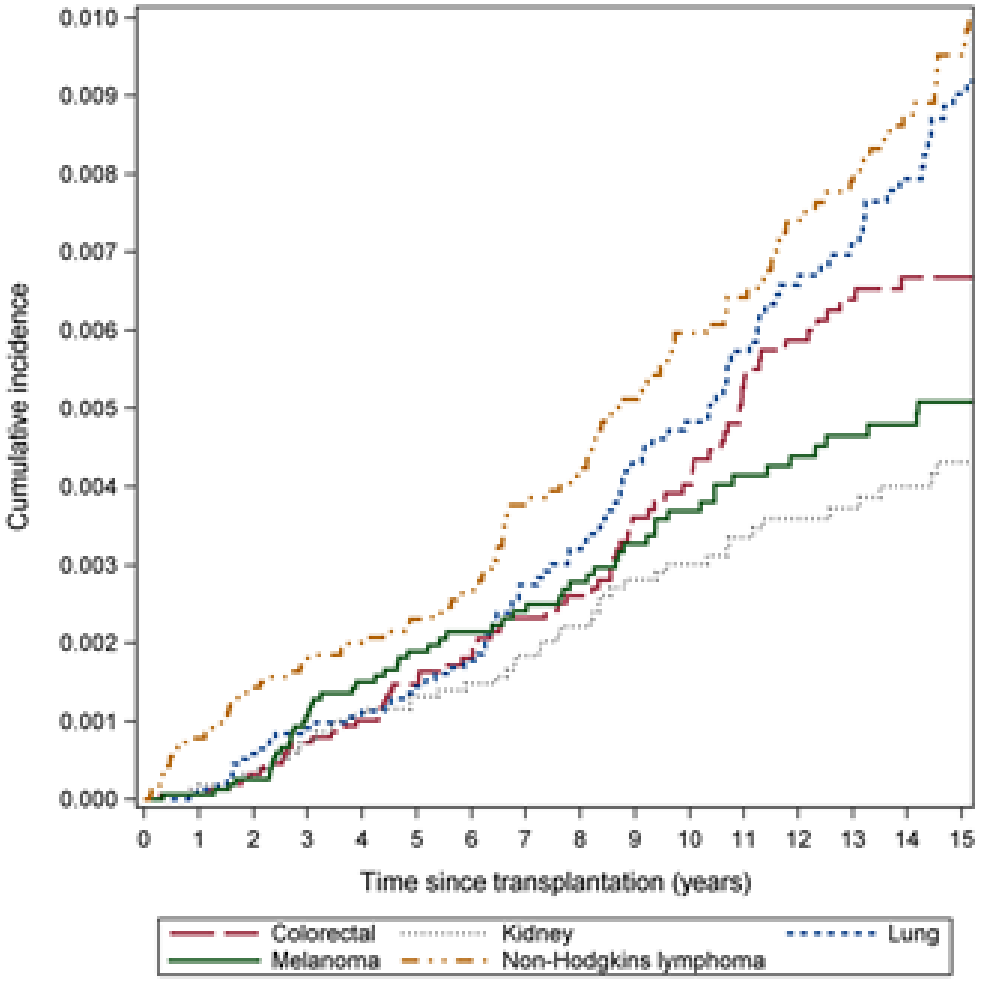
	Mortality Rate (per 100,000 pt-yrs)	SMR	95% CI
All			
Dialysis	1611	2.6	(2.5 - 2.7)
Transplant	719	2.7	(2.6 - 2.9)
Gender			
Male	1809	2.5	(2.4 - 2.6)
	764	2.6	(2.4 - 2.9)
Female	1345	3.0	(2.8 - 3.2)
	653	2.9	(2.6 - 3.3)
Age			
20-34	163	19.1	(11.1 - 30.6)
	93	11.0	(6.6 - 17.2)
35-49	455	9.8	(8.2 - 11.7)
	307	6.7	(5.6 - 8.0)
50-64	1325	5.4	(5.0 - 5.8)
	888	3.6	(3.3 - 4.0)
65+	2426	2.1	(2.0 - 2.2)
	1957	1.7	(1.6 - 1.9)
Excluding pre-existing cancers			
Dialysis	700	1.2	(1.1 - 1.3)
Transplant	673	2.6	(2.4 - 2.8)



Both relative and relative risk of death is very high, and highest for younger recipients!

Au, E (unpublished)

Common cancers causing death in transplant recipients



PTLD

Lung

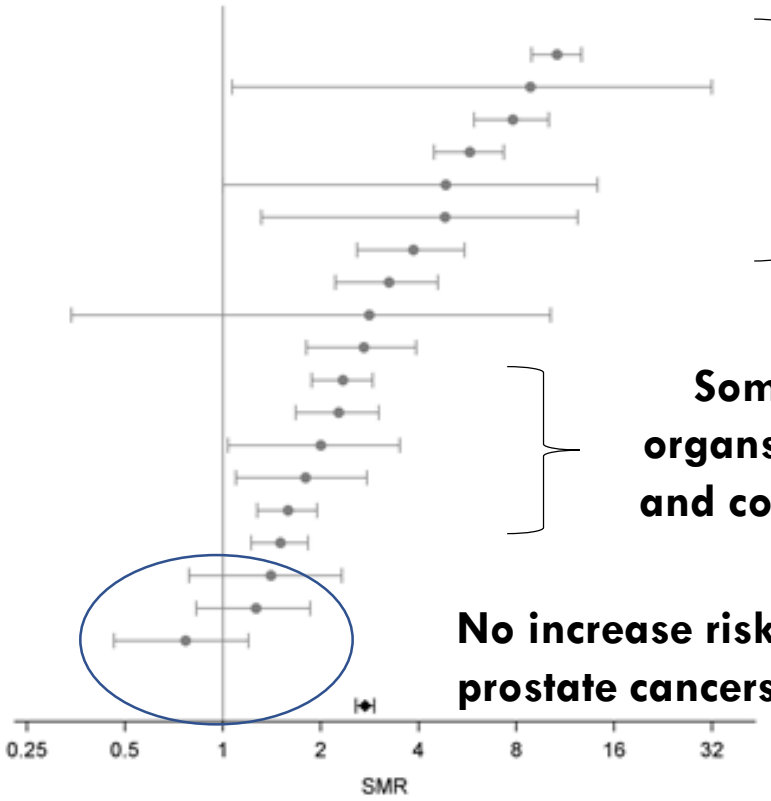
Colorectal

Melanomas

Kidney cancers

Site-specific cancer death in kidney transplant recipients

Cancer Type	Mortality Rate (per 100,000 pt-yrs)	SMR	95% CI
Non-Hogkin Lymphoma	100	10.7	(8.9 - 12.7)
Testicular	3	8.8	(1.1 - 31.9)
Kidney	46	7.8	(5.9 - 10.0)
Melanoma	52	5.8	(4.5 - 7.3)
Hodgkin Lymphoma	2	4.9	(1.0 - 14.2)
Thyroid	3	4.8	(1.3 - 12.3)
Bladder	23	3.9	(2.6 - 5.5)
Head and Neck	25	3.2	(2.2 - 4.6)
Bone	2	2.8	(0.3 - 10.2)
Gynaecological	54	2.7	(1.8 - 3.9)
Colorectal	68	2.3	(1.9 - 2.9)
Unknown Primary	37	2.3	(1.7 - 3.0)
Multiple Myeloma	9	2.0	(1.0 - 3.5)
Leukaemia	16	1.8	(1.1 - 2.8)
Other Gastrointestinal	70	1.6	(1.3 - 1.9)
Lung	79	1.5	(1.2 - 1.8)
Brain	12	1.4	(0.8 - 2.3)
Breast	50	1.3	(0.8 - 1.9)
Prostate	25	0.8	(0.5 - 1.2)
All Cancers	719	2.7	(2.6 - 2.9)

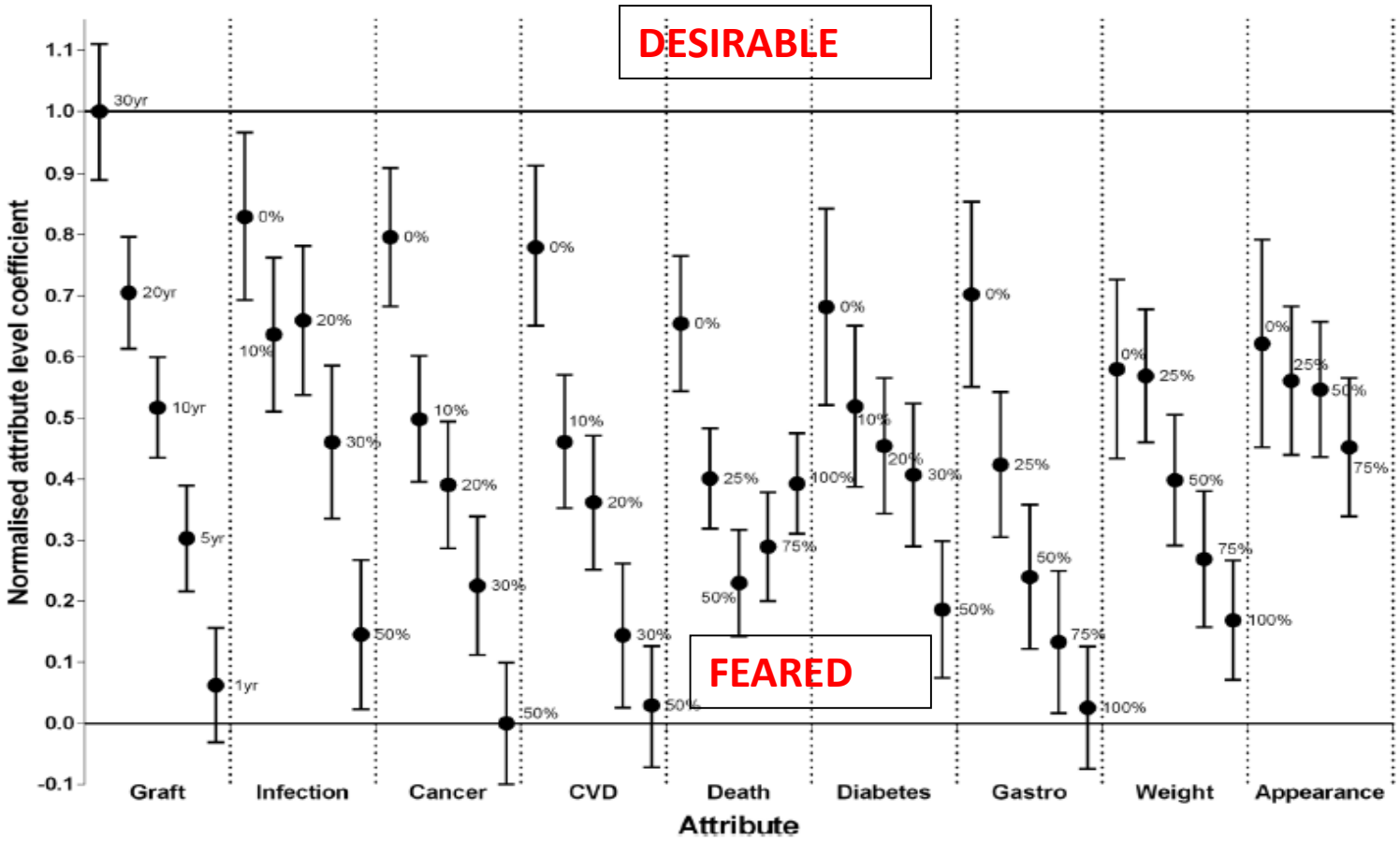


Immune driven Kidney related

Some other solid organs including lung and colorectal cancers

No increase risk for breast and prostate cancers

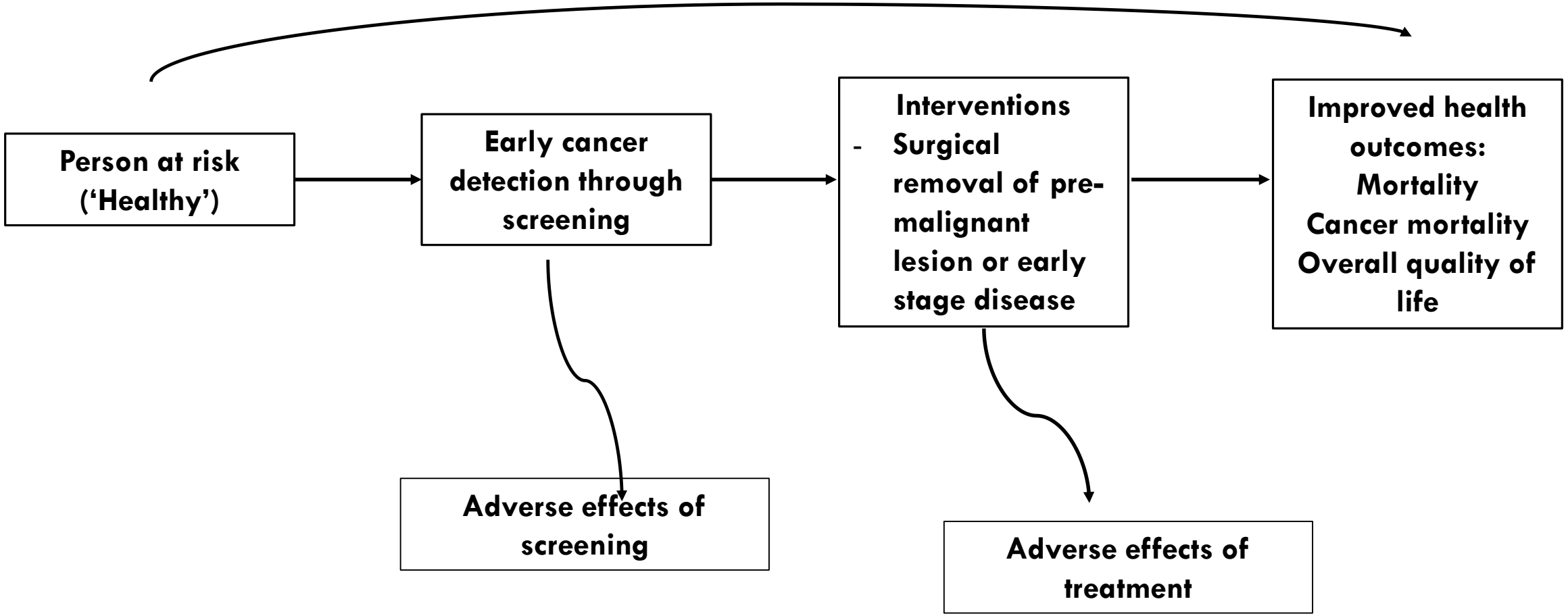
Cancer is an important outcome for kidney transplant recipients



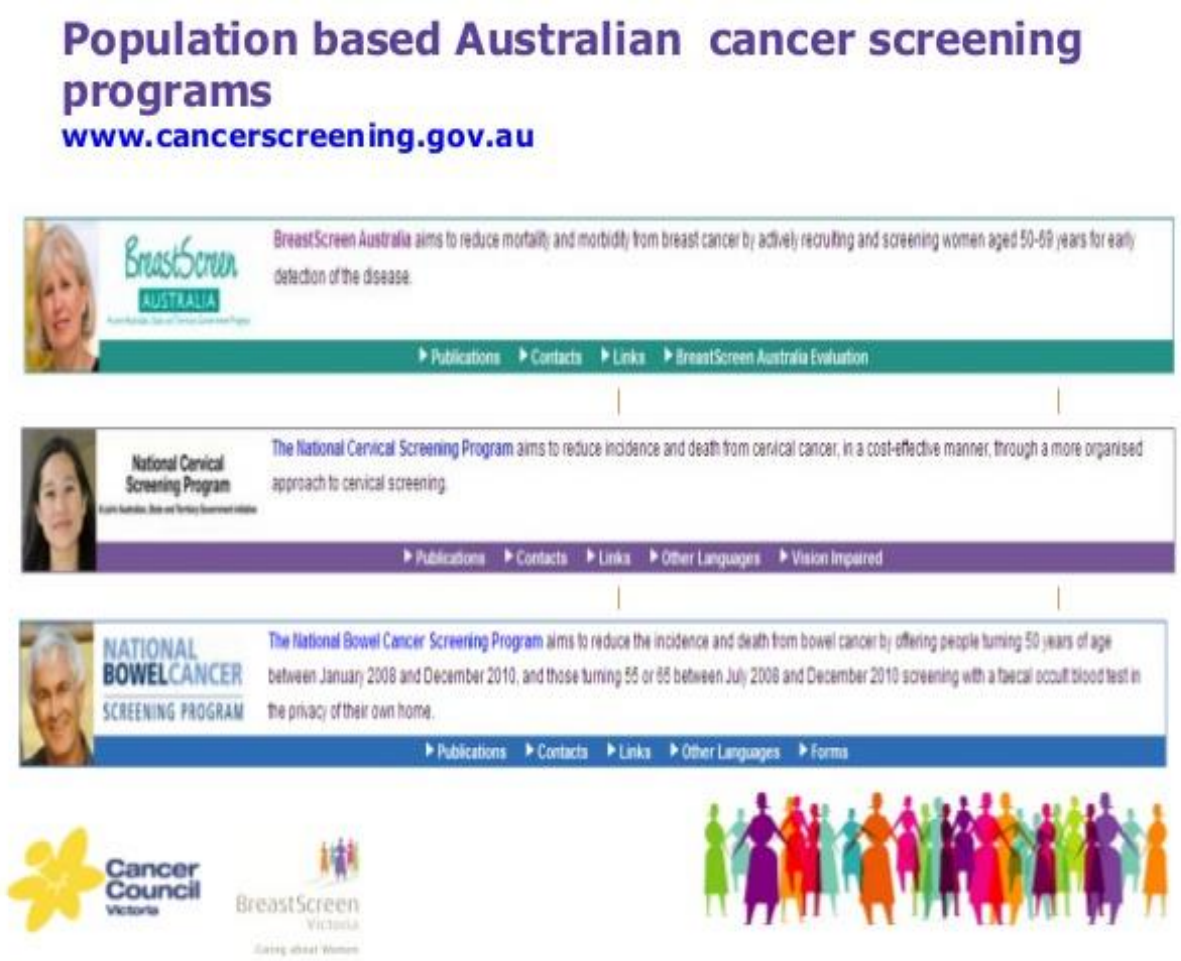
Strategies to improve outcomes

- Prevention
- Early detection through screening
- Effective treatment

Why do we screen? – the Framework



Population-based cancer screening programs in Australia



HPV 16/18 testing every 5 years for those aged 25-75 years.

Biennial mammography for those aged 50 years and above.

Biennial faecal immunochemical testing for those aged 50 years and above.

WHO guiding principles of an effective cancer screening program

- The condition should be an important health problem
- The natural history of the disease should be well-understood
- There should be an accepted treatment for patients with the recognised disease
- The test should be accurate
- The test should be acceptable to the population
- Cost effective

What does the guidelines say?

Table 4. Recommendations for cancer screening in renal transplant recipients

Cancers	Recommendation	RCT Evidence that Earlier Intervention Works	Test Performances	Cost-Effectiveness, ICER ($/LYS)
Breast	Annual or biennial mammography for all women older than 50 yr Women between 40 and 49 could still undergo screening, but no evidence for or against screening at this age (10,12)	Nil	No data	32,000 (32)
Colorectal	Annual FOBT and/or 5-yearly flexible sigmoidoscopy for individuals older than 50 yr (10,12)	Nil	No data	25,189 (32)
Cervical	Annual cytological cervical cancer screening and pelvic examination once sexually active (10,12)	Nil	No data	No data
Prostate	Annual DRE and PSA measurement in all male renal transplant recipients older than 50 yr (10,12)	Nil	No data	56,850 (32)
Hepatocellular	α-Fetoprotein and ultrasound performed every 6 mo in high-risk individuals, but no firm confirmation (10,12)	Nil	No data	No data
Skin	Monthly self-skin examination, total body skin examination every 6 to 12 mo by expert physicians and dermatologists (11,12)	Nil	No data	No data
Renal	No firm recommendation; some suggested regular ultrasonography of the native kidneys (10,12)	Nil	No data	No data

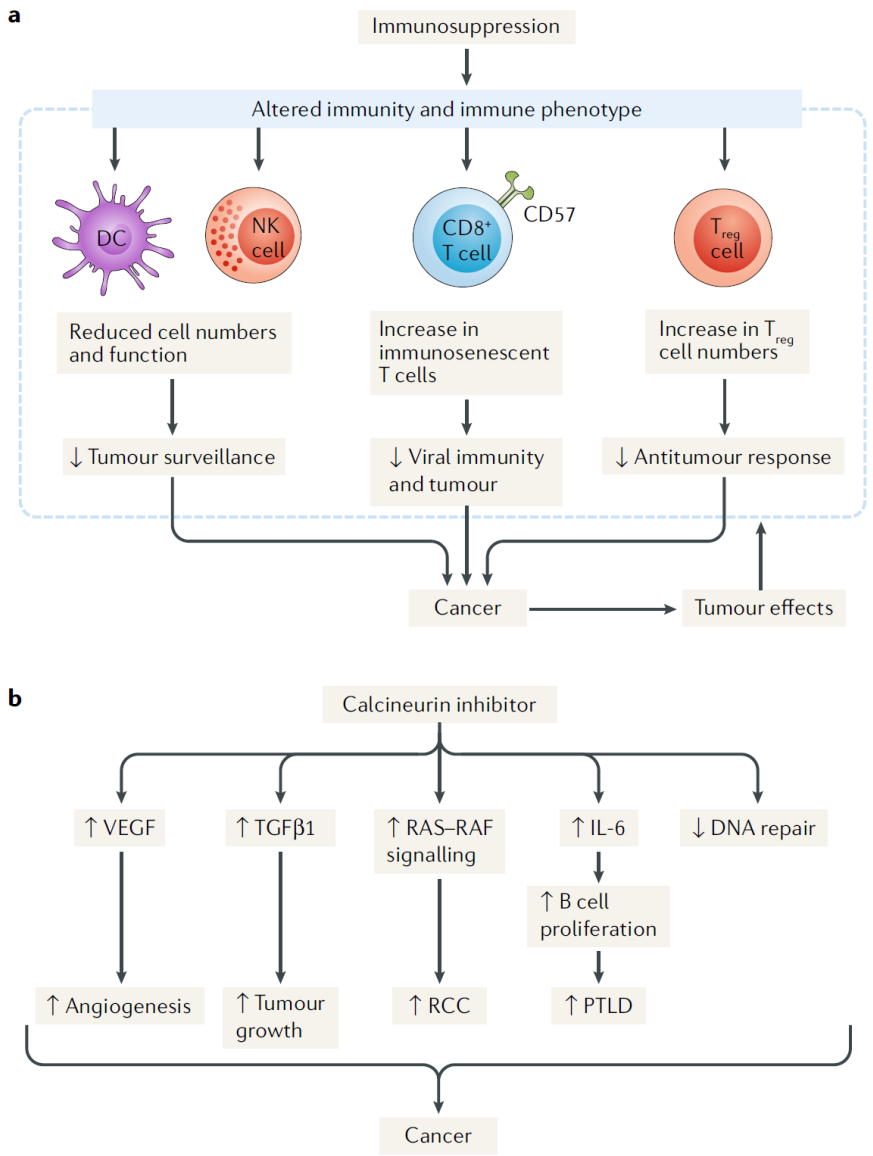
Evidence free zone!!

Wong CJASN 2008

So, should we screen for cancer after transplantation?

- The condition should be an important health problem Yes
- The natural history of the disease should be well-understood ?
- There should be an accepted treatment for patients with the recognised disease ?
- The test should be accurate ?
- The test should be acceptable to the population ?
- Cost effective ?

Natural history of cancer in kidney transplant recipients



Cancer development may be rapid and much more aggressive in kidney transplant recipients than in the general population

Effective cancer treatment after transplantation?

- Immunosuppression reduction
- Chemotherapeutic agent:

i. Fear of drug to drug interaction
ii. Fear of acute rejection
iii. Fear of nephrotoxicity

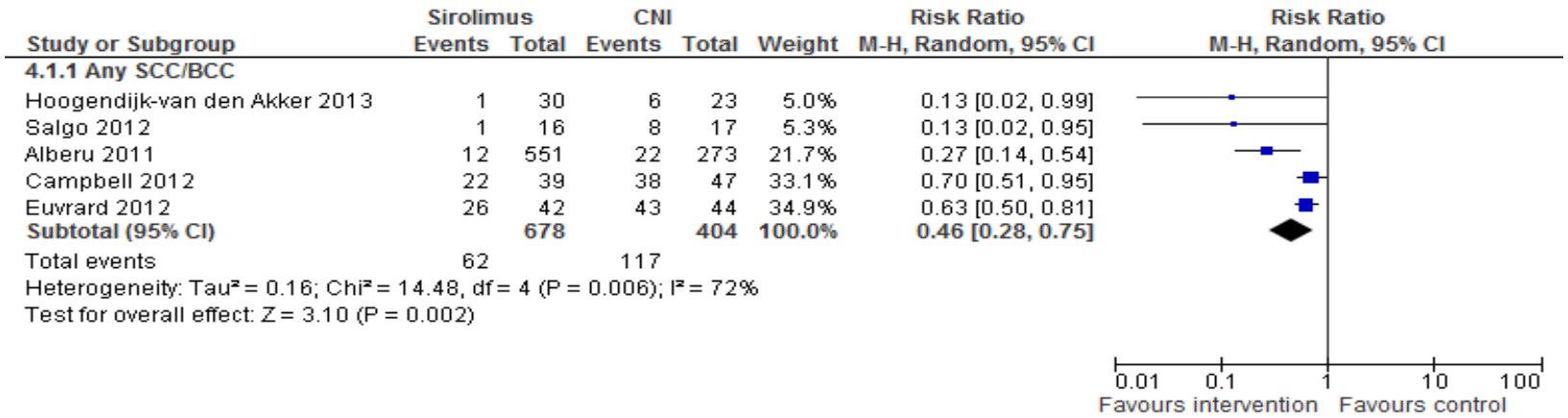
Role of mTORIs?

- 69 year old men
- Prior history of SCC before transplantation
- Experienced early rejection (vascular rejection)
- Receive routine skin checks by his dermatologist
- Found to have recurrent SCC in scalp
- Treated with surgery and radiotherapy
- Should we switch to mTORIs?

Outcomes – Conversion to mTORis

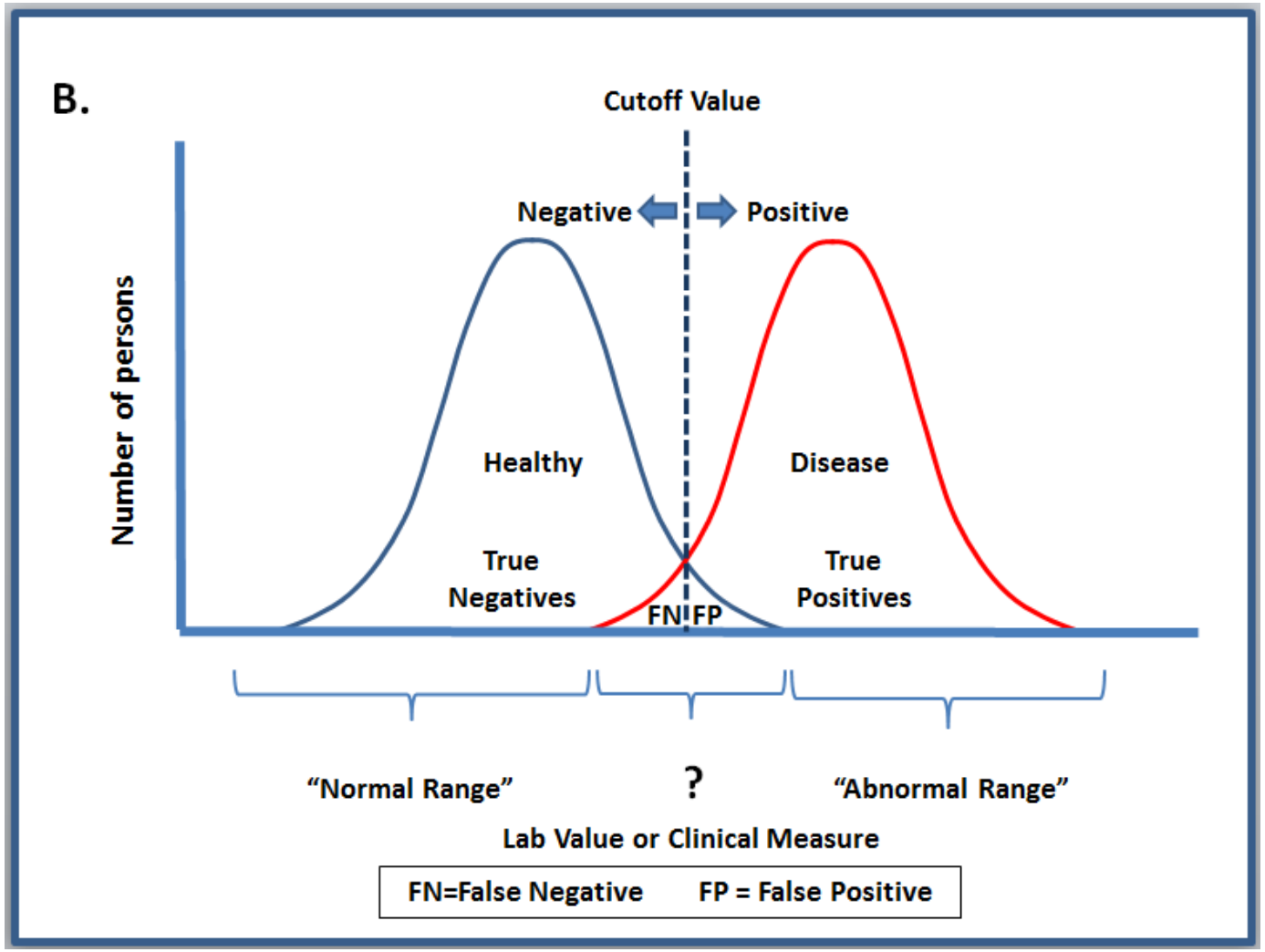
Immunosuppression

	N	n	RR (95% CI)	Intervention	Quality of reporting
Reduction of cancer incidence	5	1080	0.46 (0.28, 0.75)	mTORis vs. CNIs	Very low

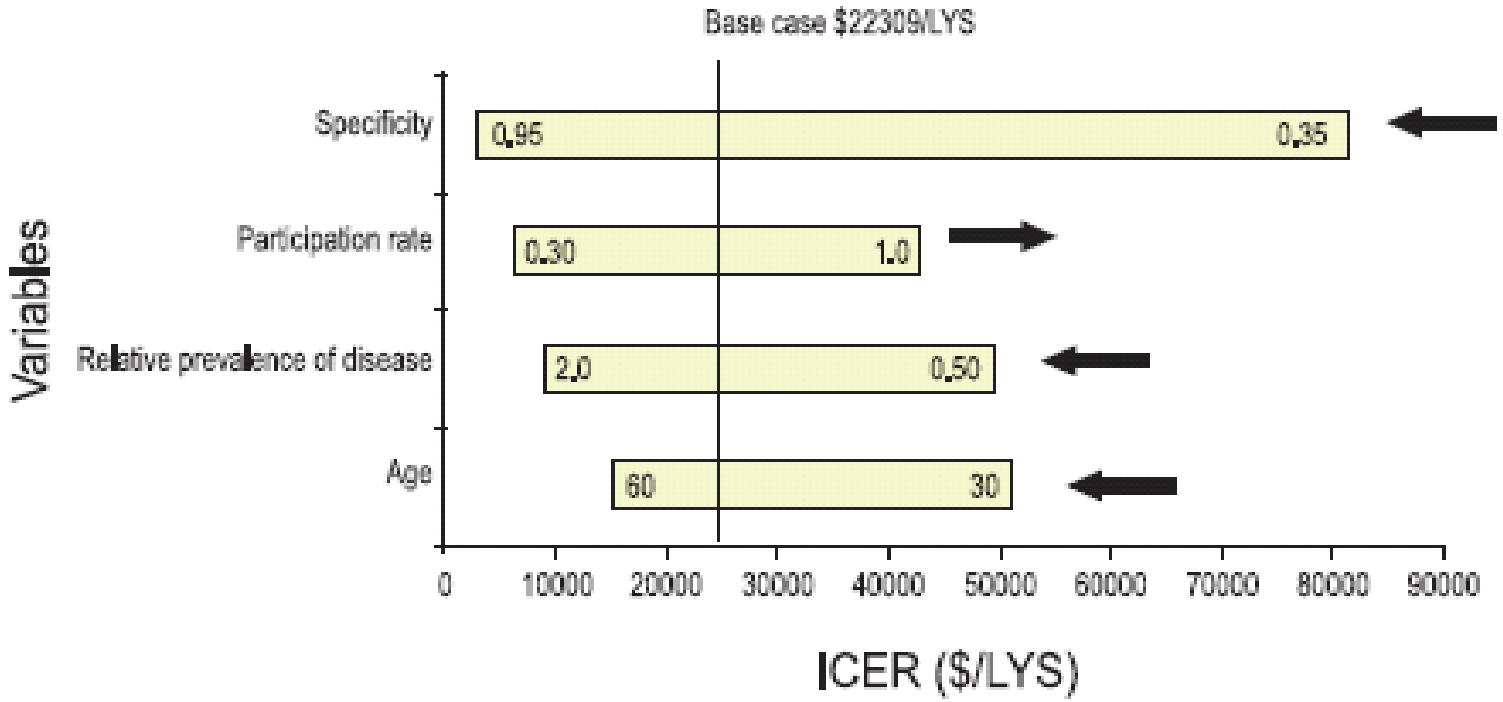


James et al – Transplantation (Under Review)

Accuracy of the screening test



Bowel cancer screening in kidney transplant recipients



Major uncertainty:

Test performance characteristics of the screening tool!!!

(*Transplantation* 2008;85: 532–541)

Bowel cancer screening in kidney transplant recipients

Screening for colorectal cancer and advanced colorectal neoplasia in kidney transplant recipients: cross sectional prevalence and diagnostic accuracy study of faecal immunochemical testing for haemoglobin and colonoscopy

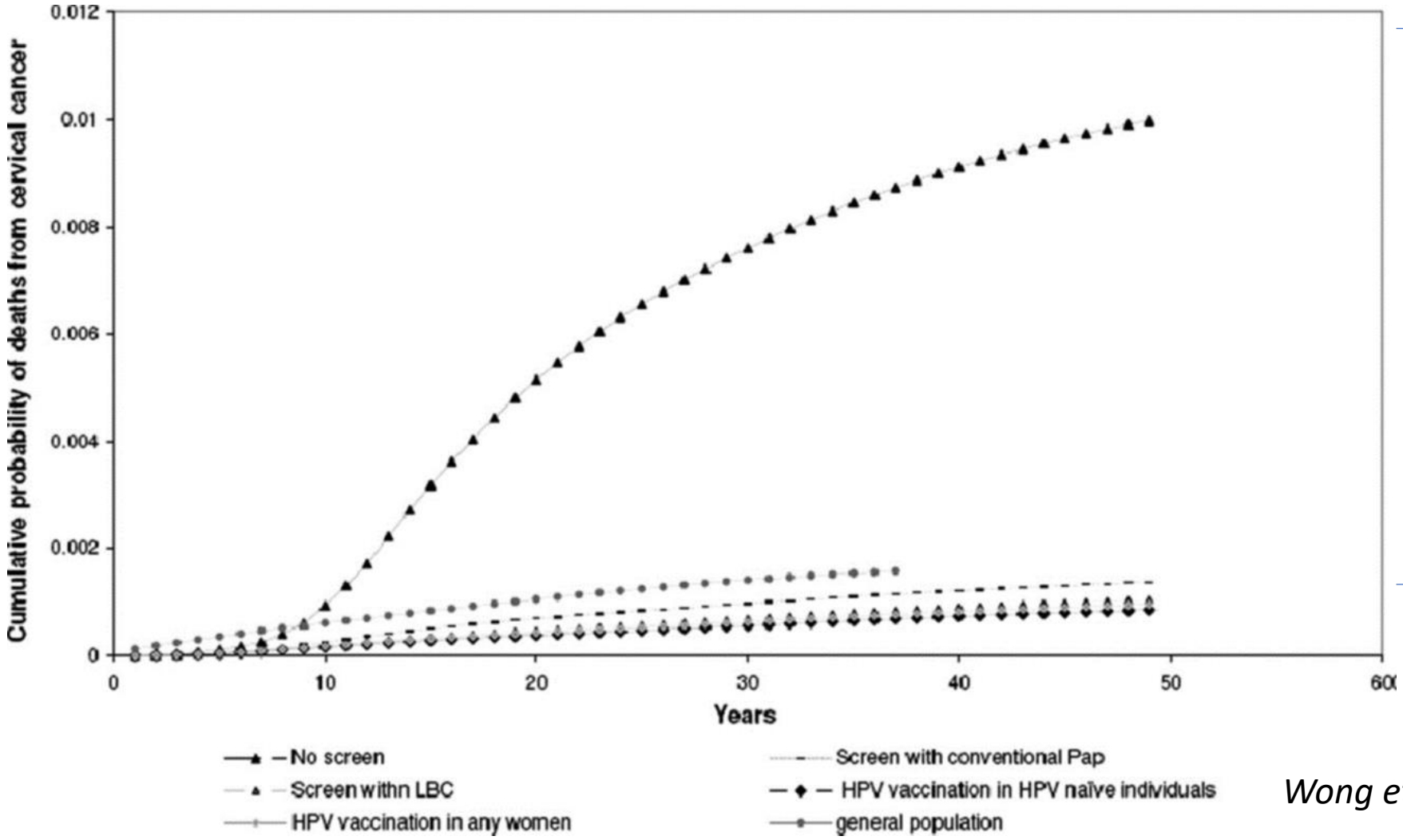
Parameter	Point estimate (95% CI)
Sensitivity (%)	31.0 (15.3 to 50.8)
Specificity (%)	90.5 (85.6 to 94.2)
Positive predictive value (%)	32.1 (15.9 to 52.4)
Negative predictive value (%)	90.1 (85.1 to 93.8)
Positive likelihood ratio	3.27 (1.64 to 6.52)
Negative likelihood ratio	0.762 (0.595 to 0.977)
Diagnostic odds ratio	4.29 (1.75 to 10.60)

Similar to that of the general population….

Cervical cancer screening

- 19 year old woman
- Sexually active
- Received a kidney transplant from mother one year ago
- Had HPV vaccination at the age of 15 years as part of the National HPV vaccination program.
- Should this woman be screened, if so, how often?

Benefits of cervical cancer screening in transplant recipients



Gains are substantial compared with no screening

Wong et al Transplantation 2009

Breast cancer screening

- 65 female
- Received a deceased donor kidney transplant 5 years ago
- Regular breast screening using Mammography every 2 years
- All screen findings are negative
- Should she continue to receive screening ?

Breast cancer screening

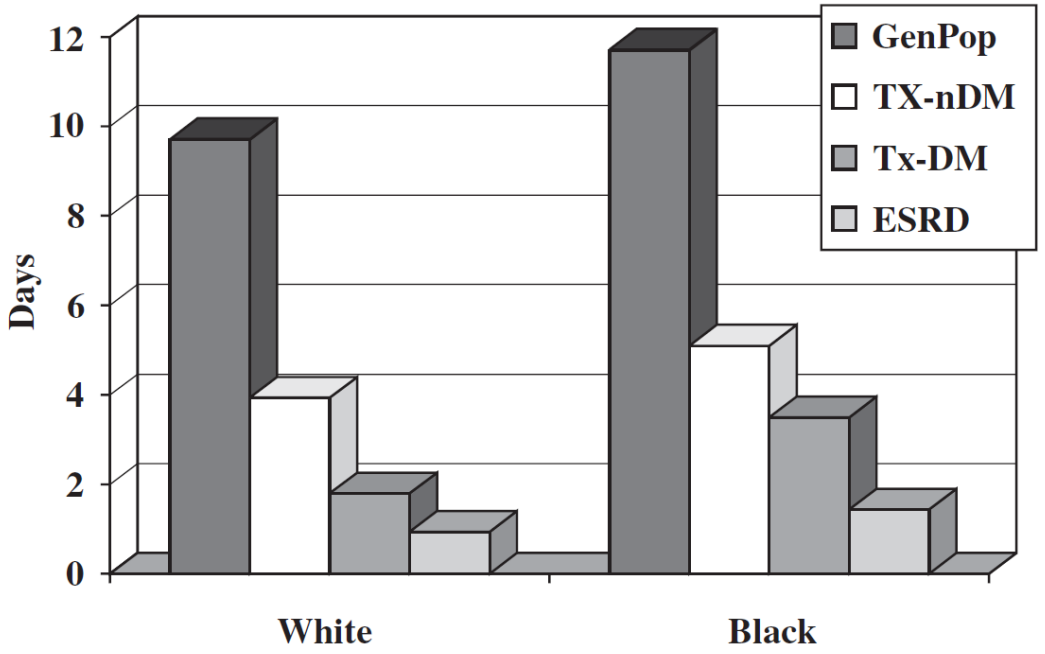


Figure 1: Days of life saved with screening for breast cancer in the White and Black female populations.

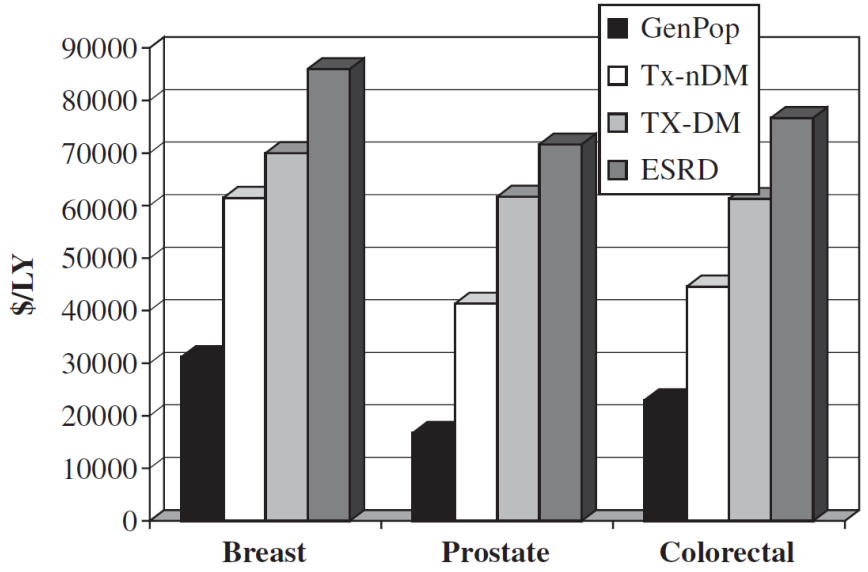


Figure 5: Cost per life year gained ($/Ly) with screening for breast, prostate and colorectal cancer in the Black male population.

American Journal of Transplantation 2003; 3: 619–625
Blackwell Munksgaard

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Screening for Prostate, Breast and Colorectal Cancer in Renal Transplant Recipients

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Screening for renal cancers

Table 1. Recommendation for patient screening of the native kidneys in renal transplant patients according to the Bosniak renal cyst classification (11)[a]

1. All patients should have an ultrasound screening of their native kidneys once a year irrespective of ACKD.
2. Patients with ACKD and cysts according to Bosniak category I and II (benign simple cysts): Ultrasound screening twice a year; CT scan in the case of progressive lesions.
3. Patients with ACKD and cysts according to Bosniak category IIF (moderately complex cystic lesions): Ultrasound screening four times a year; CT or MRI scan once a year; nephrectomy in the case of progressive lesions, even if not reaching category III or IV.
4. Patients with ACKD and cysts according to Bosniak category III ("indeterminate" cystic masses) and IV (clearly malignant cystic masses): Nephrectomy.
5. Patients with ACKD in general: Generous indication for nephrectomy even in the lower categories, if progression occurs, because the original sense of the Bosniak classification (to preserve renal tissue by exact preoperative diagnosis) has lost its importance in patients with end-stage renal failure. This is true especially for cystic lesions of category IIF.

[a]ACKD, acquired cystic kidney disease; CT, computed tomography; MRI, magnetic resonance imaging.

What is the evidence behind these recommendations?

Table 4. Marginal costs and benefits of screening renal cell carcinoma (expanding from biennial to annual screening)

Screening strategies	Total benefits (LYS)	Total costs ($)	Average cost-effectiveness ratio ($/LYS)	Marginal costs ($)	Marginal benefits (LYS)	Marginal cost-effectiveness ratio ($/LYS)
Annual	13.64598	303 000	22 204	400	0.000488	833 333
Biennial	13.64550	302 600	22 175			

All recipients

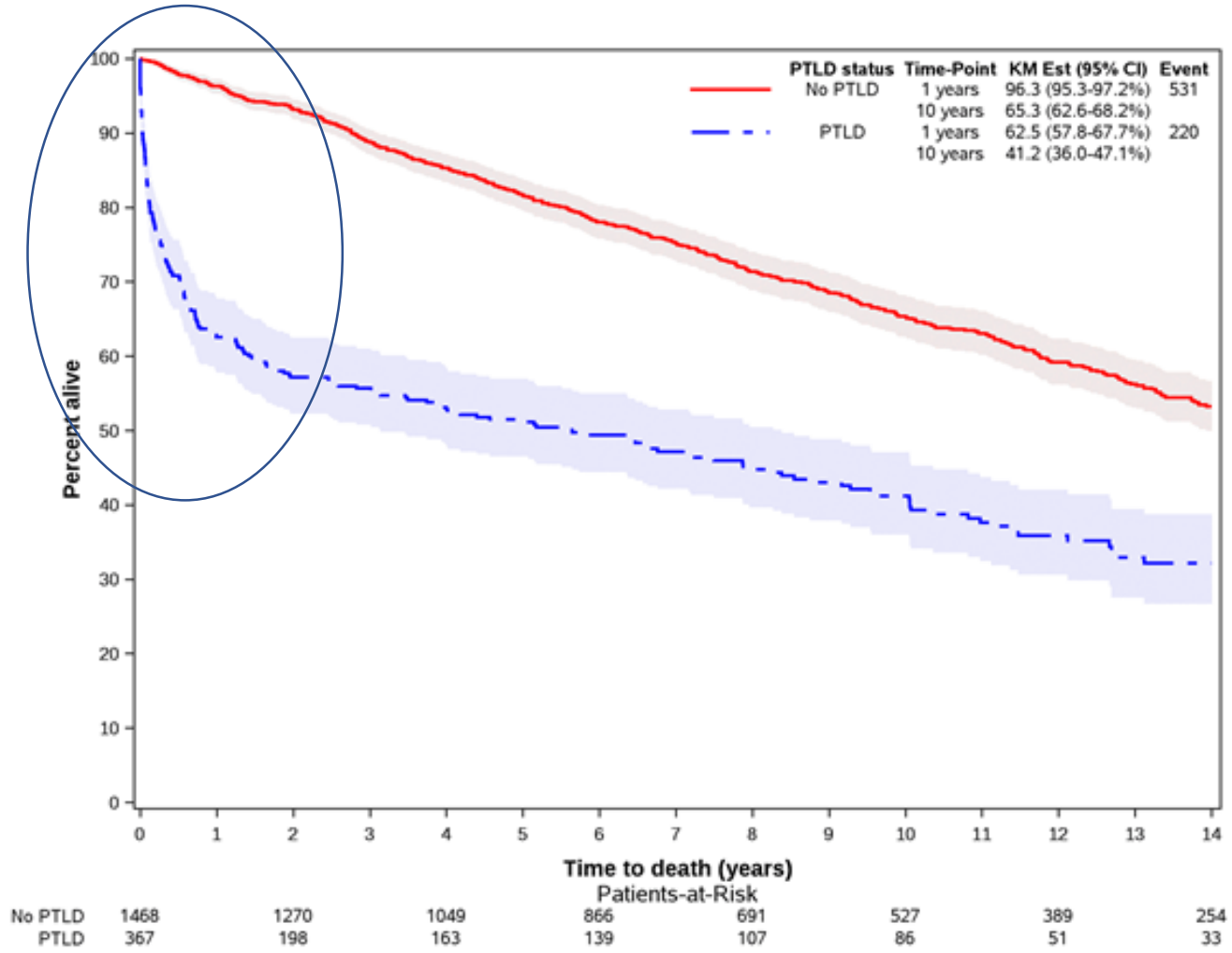
Table 5. Total and incremental costs and benefits of screening renal cell carcinoma in the high-risk kidney transplant population

High-risk populations	Screening strategies	Total benefits (LYS)	Total costs ($)	Incremental benefits (LYS)	Incremental costs ($)	Incremental cost-effectiveness ratio (ICER) ($/LYS)
Prior history of renal cancer	No screening	13.57948	300 008			
	Annual	13.59719	301 568	0.01771	1560	88 085
	Biennial	13.59518	301 018	0.01570	1010	64 331
Familial or hereditary disease such as tuberous sclerosis	No screening	13.59883	300 530			
	Annual	13.61278	301 931	0.01395	1401	100 430
	Biennial	13.61077	301 460	0.01197	930	77 694
History of analgesic nephropathy	No screening	13.58538	300 167			
	Annual	13.60193	301 679	0.0165	1512	91 636
	Biennial	13.59993	301 153	0.0145	986	68 000
Acquired cystic kidney disease	No screening	13.55289	299 291			
	Annual	13.57571	301 069	0.02282	1778	77 914
	Biennial	13.57368	300 411	0.02079	1120	53 872

All screening strategies (annual or biennial) were compared with no screening.

High risk

PTLD

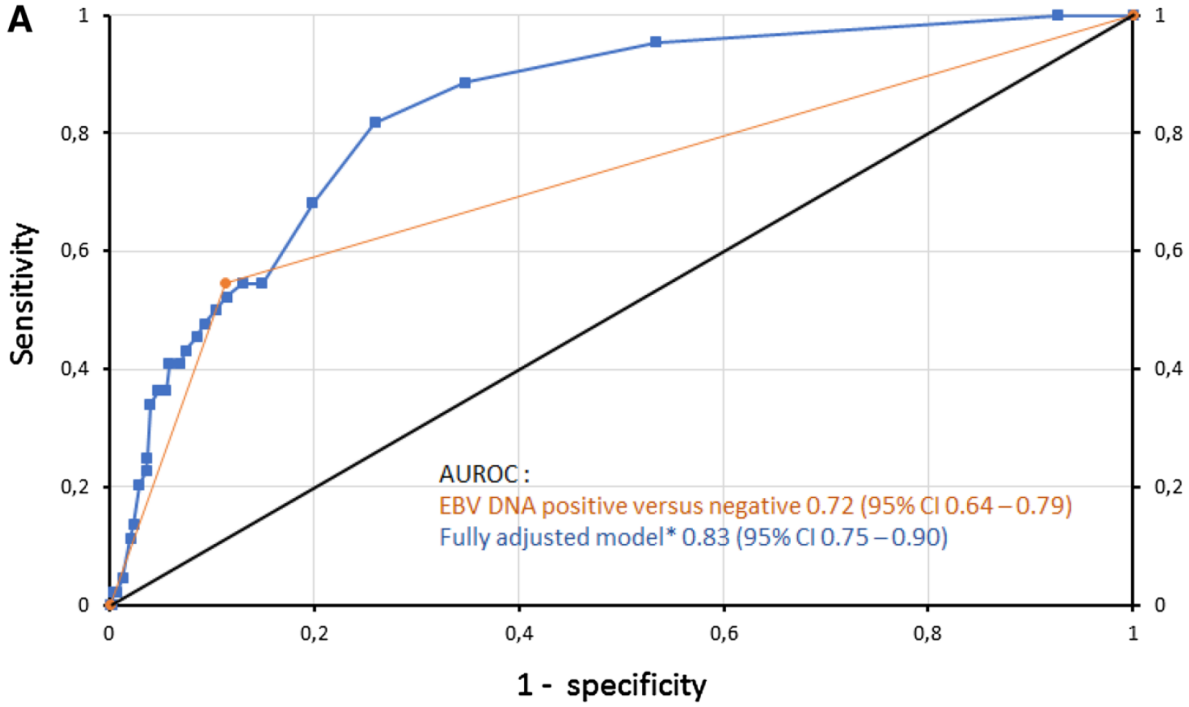


PTLD carries a very poor prognosis. Only 60% of those diagnosed with PTLD survived after 1 year of diagnosis.

KI in press Francis et al

Screening for PTLD

- Emerging EBV viraemia is considered a marker of early PTLD
- Many have advocated routine screening to detect early disease before the development of fulminant lymphoma

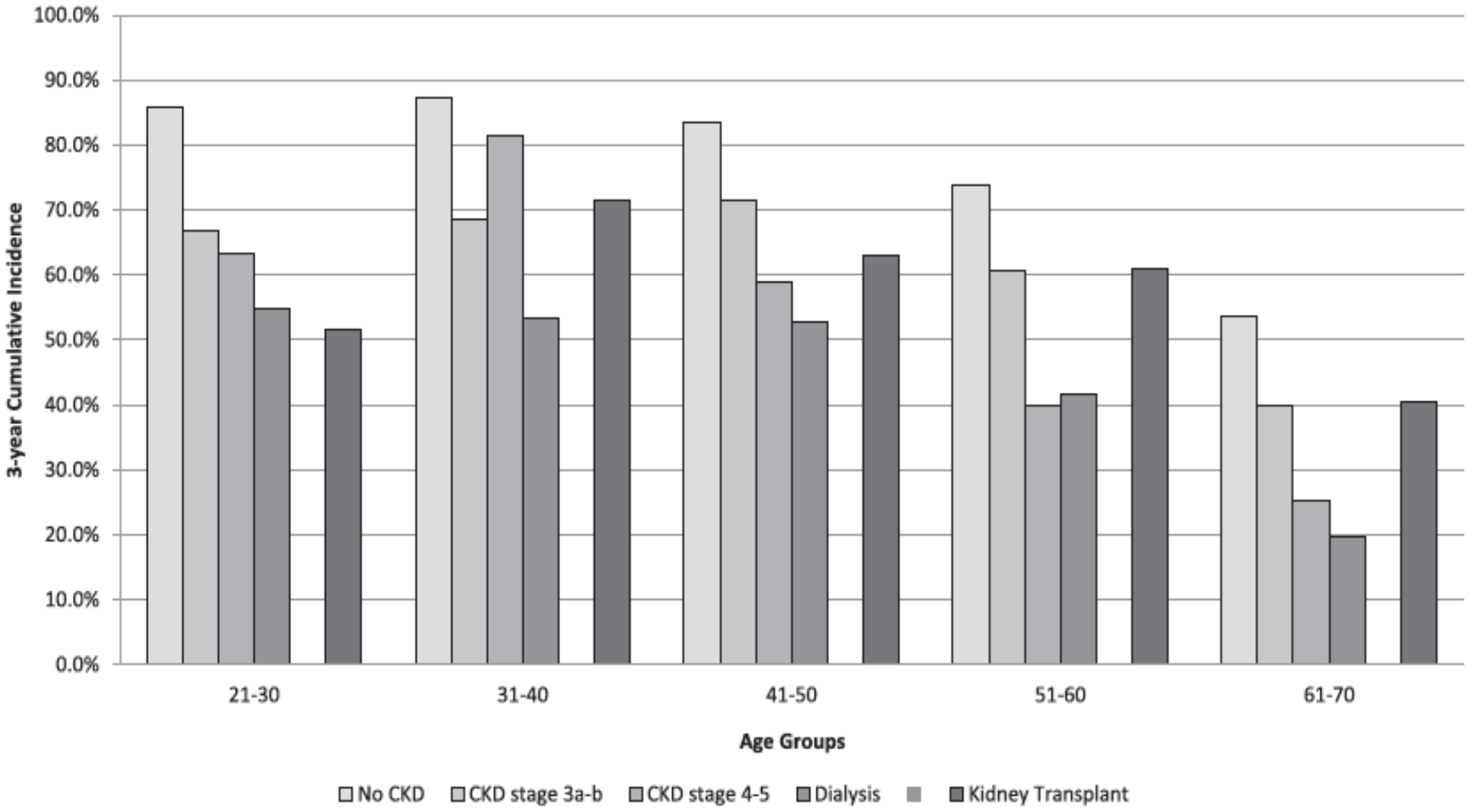


*Model includes adjustment for age, gender, year of transplant, number of transplants, high risk status (D+/R- for SOT), hemoglobin, thrombocytes, and CRP

EBV viraemia

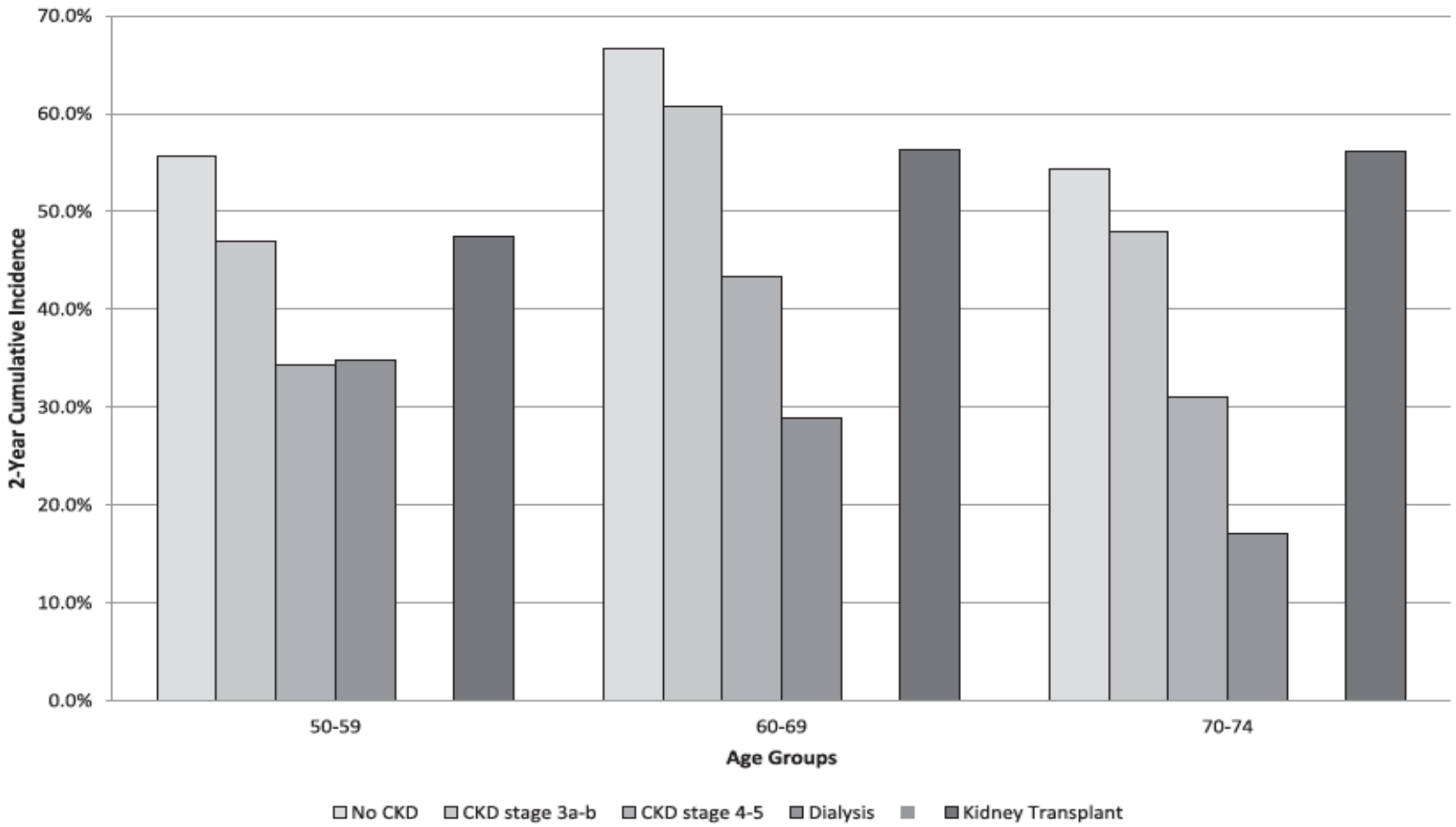
1. When used alone – not a great test
2. When used in the context of other clinical events, both the test sensitivity and specific increase

Patient preferences for cancer screening – cervical cancer screening

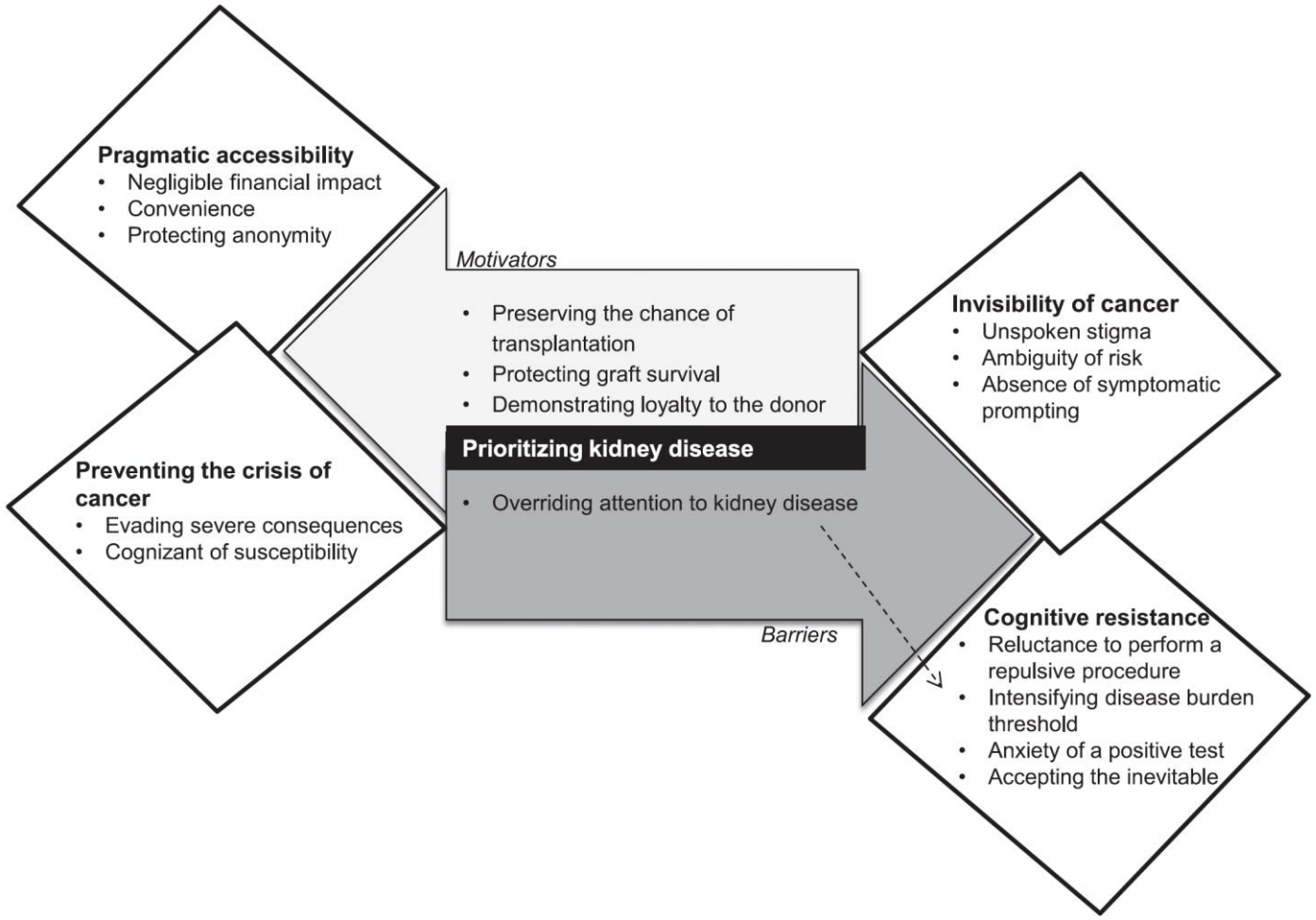


Wong G et al CJASN 2016; Ontario data from The Institute for Clinical Evaluative Sciences (ICES)

Patient preferences for cancer screening – breast cancer screening

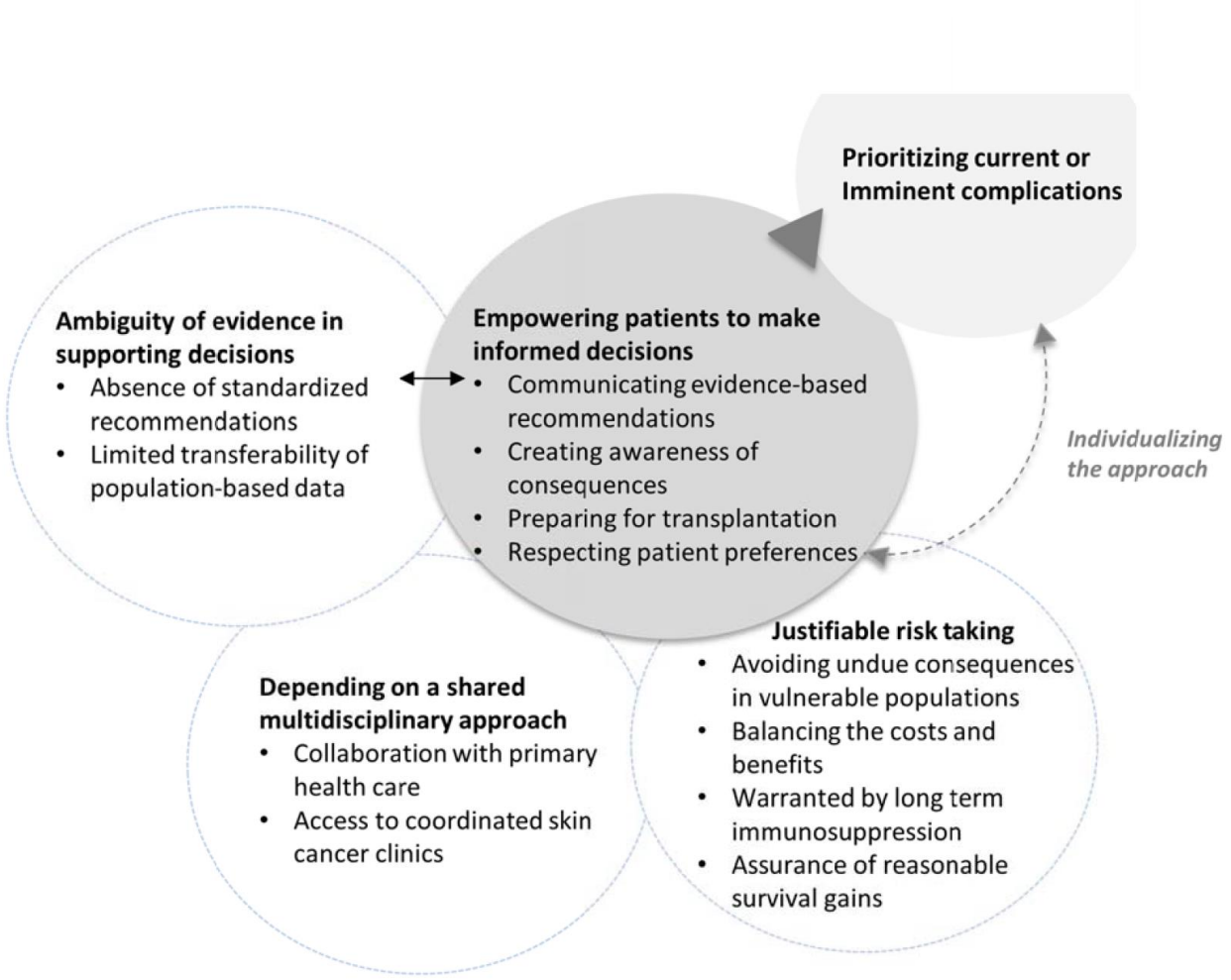


Beliefs and attitudes to bowel cancer screening



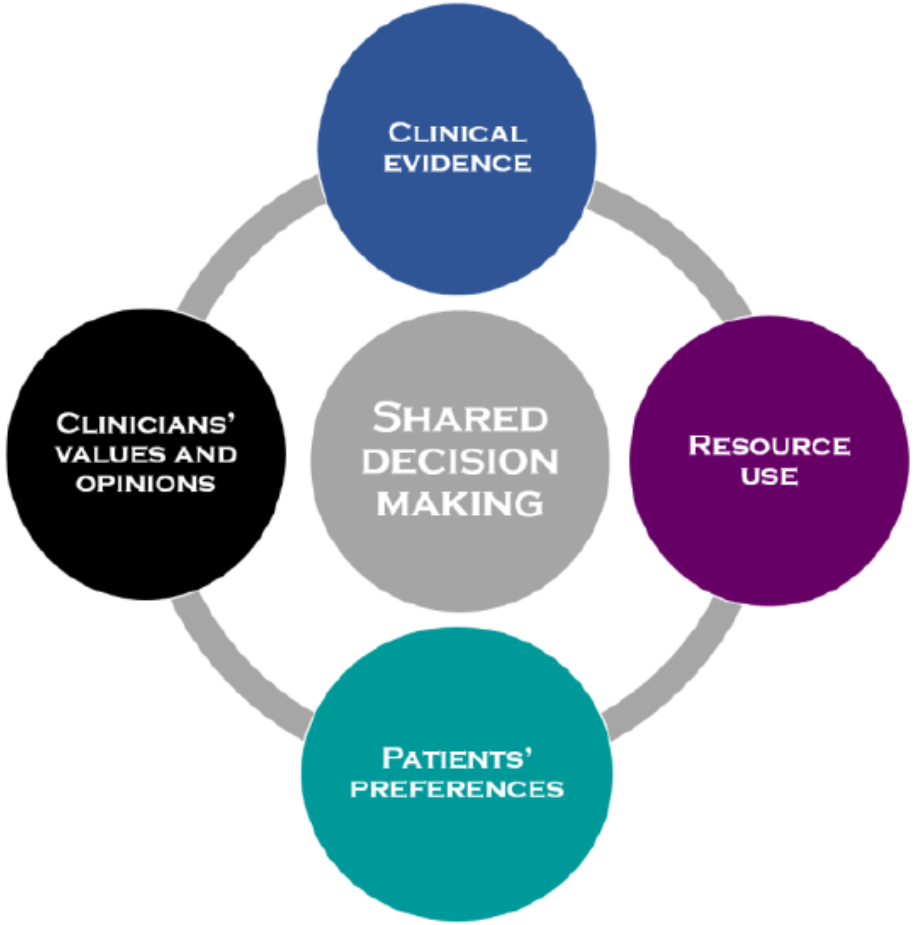
Clin J Am Soc Nephrol 12: 568–576, April, 2017

Nephrologists perspective on cancer screening



- **Uncertainties in existing evidence**
- **Lack of standardised guidelines and recommendations**
- **Respect patients' choices**
- **Advocating for individualised approach**
- **While understanding the need for early cancer detection.**

Evidence framework to inform shared decision making in cancer screening



Thank you

- Eric Au
- Laura James
- Martin Howell
- Anna Francis