GoldNet Research Online Journal Club

Genetic Testing in Primary Care

Thank you for joining, we will commence shortly.
If you are not already a GoldNet member,
please sign up using the QR code.

Prof. Nick Zwar
Executive Dean, Faculty of Health Sciences and Medicine, Bond University & Chair of GoldNet

Assistant Prof. Loai Albarquoni
NHMRC Emerging Leader Fellow, Institute for Evidence Based Healthcare, Bond University

Prof. Jon Emery
Herman Professor of Primary Care Cancer Research, Centre for Cancer Research University of Melbourne

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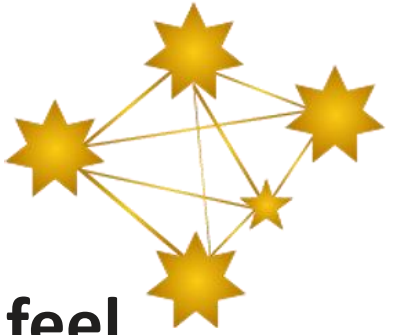
GoldNet Research
The Gold Standard in Primary Care Research

In the spirit of reconciliation, we acknowledge the Kombumerri people, the traditional Owners and Custodians of the land on which GoldNet and partners are based. We pay respect to Elders past, present and emerging.

Journal Club Housekeeping



- **A member of our team is keeping an eye on the chat – please feel free to add comments or questions at anytime**
- **During the presentations, please keep your microphone turned off**
- **For the Q&A session, we encourage you to turn on your camera and microphone when you have questions**

Journal Club Agenda

- **Welcome & Case Study**
  - **Prof Nick Zwar** (Chair of GoldNet Steering Committee)
- **Overview of article:** *Population DNA screening for medically actionable disease risk in adults*
  - **Assistant Prof Loai Albarqouni**
- **Group Discussion**
  - **Prof Jon Emery**
  - **Prof Nick Zwar**
  - **Assistant Prof Loai Albarqouni**
- **Conclusion**

A link to the journal article is available in the chat. It is open access.

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Case Study

Case Study

- 51 year old man presents for check up
- New patient recently returned from United States
- Non smoker, 2 glasses wine Friday and Saturday night
- Past history: migraine, irritable bowel syndrome
- Weight 78kg 178cm BMI 24.6, Office BP 132/76

Family history

- Older brother diagnosed with early-stage CRC at age 59
- Father diagnosed with prostate cancer age 78

Preventive activities over the lifecycle – **Adults**

Screening Case-finding

Activity/topic	Age group														Frequency	Notes
	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	≥80		
Cancer																
Breast															Screening: Every two years Case-finding: At least every two years	Screening: Women at average risk or slightly higher than average risk of breast cancer should participate in mammographic screening from ages 50 to 74 years as part of the national BreastScreen program. Case-finding: Undertake mammographic screening from ages 40 to 74 years for women at moderately increased risk.
Cervical															Every five years	Women and people with a cervix who are aged between 25-74 years, have ever had sexual contact and who are eligible for screening should have an HPV screening test for cervical cancer. This can be on a self-collected vaginal sample or on a clinician-collected sample.
Colorectal															Every two years	Immunochemical faecal occult blood testing (iFOBT) every two years is recommended starting at age 45 years and continuing to age 74 years for those at average risk of colorectal cancer.
Prostate															See chapter for frequency	See chapter for individual recommendations.
Skin															See chapter for frequency	See chapter for individual recommendations.
Cardiovascular																
Atrial fibrillation (AF)															Opportunistically	Opportunistic clinical palpation or auscultation to detect asymptomatic AF in people aged 65 years or more.
Cardiovascular disease risk	BP only	BP only	BP only	BP only	BP only	BP only									Blood pressure (BP) (18+ years) opportunistically; no more than every two years. CVD risk (age 45 - 79) every five years unless risk factors worsen.	See chapter for individual recommendations.
Infectious diseases																
Immunisation	Immunisation is recommended at particular ages throughout life, according to the Australian Immunisation Handbook.														See chapter for frequency	See chapter and Australian Immunisation Handbook schedule for recommendations.
Sexually transmitted disease															Opportunistically if indicated (evidence is unclear on testing interval).	Screening for chlamydia and gonorrhoea is recommended in all sexually active women 24 years or younger but only in those who are at increased risk (see Box 1) in women 25 years or older.
Injury prevention																
Bullying and child abuse															Opportunistically	See chapter for individual recommendations.
Mental health																
Alcohol															Every two years	Screen adults aged ≥18 years, including pregnant women, for unhealthy alcohol use. The Alcohol Use Disorder Identification Test – Consumption (AUDIT-C) tool can be used to assess this. Provide persons engaged in risky or hazardous drinking with brief behavioural counselling interventions to reduce unhealthy alcohol use.
Anxiety															As required	See chapter for individual recommendations.
Dementia															Opportunistically	See chapter for individual recommendations.
Depression															See chapter for frequency	See chapter for individual recommendations.
Gambling															Opportunistically	In patients experiencing stress, mental health issues or substance use problems; in people experiencing or perpetrating domestic violence; in people experiencing relationship breakdown; and/or in people with symptoms of compulsive gambling (see Box 1), ask about gambling behaviours (eg sports betting, wagering, card playing, pokies, casino gambling, online gambling). For example, 'In the past 12 months, have you or someone you are close to ever had issues with gambling?'
Smoking and nicotine vaping															At every opportunity starting from the age of 10 years	Ask patients whether they are currently smoking and document their smoking status. Also ask about and document the use of vaping products.
Metabolic																
Diabetes															Determined by individual risk. See chapter for recommendations.	General population of average risk (for screening of high-risk and highest-risk populations, see Diabetes chapter).
Overweight and obesity															Opportunistically	Assess height, weight and calculate BMI with caution in adults without a known eating disorder and who are not pregnant.
Physical activity															Every two years	Ask questions about frequency, duration and intensity of physical activity and sedentary behaviour.
Musculoskeletal disorders																
Osteoporosis															Do not routinely repeat BMD + FRAX® within two years except in special circumstances.	Use FRAX® to calculate absolute fracture risk in people aged ≥50 years with lifestyle and non-modifiable risk factors (eg parent with hip fracture). When the FRAX® risk for major osteoporotic fracture (MOF) is ≥10%, refer for dual energy X-ray absorptiometry (DXA). If the risk for MOF is <10%, DXA is not recommended. Refer for BMD assessment by DXA for people aged ≥50 years with diseases/chronic conditions/medications associated with increased fracture risk. Restratify risk with FRAX® after DXA using BMD reading and treat when: the BMD T-score is ≤−2.5, or when the BMD T-score is between −1.5 and −2.5 and the FRAX® risk for MOF is ≥20% and/or the hip fracture risk is ≥3%.
Metabolic																
Preconception															See chapter for frequency	See chapter for individual recommendations.
Pregnancy - First antenatal visit															See chapter for frequency	See chapter for individual recommendations.
Pregnancy - During pregnancy															See chapter for frequency	See chapter for individual recommendations.
Interconception															See chapter for frequency	See chapter for individual recommendations.
Perinatal mental health															See chapter for frequency	See chapter for individual recommendations.
Miscellaneous																
Frailty															Every 12 months (screening). Every one - three years (case finding).	Consider screening as part of an assessment of elderly patients. Case find as an assessment of patients (age 65-74) with risk factors.

Investigation Results

- Lipids
  - Fasting cholesterol 3.7mmol/L, Triglycerides 0.5 mmol/L
  - HDL-C 1.5 mmol/L, LDL-C 2.0 mmol/L, TC/HDL-C 2.5
- Prostate
  - PSA Total 0.88 ug/L
- Diabetes
  - HbA1c 5.6%
- Colorectal cancer
  - FOBT negative

Patient asks if he should be tested for Lynch Syndrome

Article Overview

By Assistant Professor Loai Albarquoni, from the Institute for Evidence-Based Healthcare, Bond University.

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Griffith UNIVERSITY Queensland, Australia

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Check for updates

Population DNA screening for medically actionable disease risk in adults

Australia will take a world-first step towards offering preventive DNA screening through the public health care system

Paul A Lacaze*[1]
Jane Tiller*[1]
Ingrid Winship[2,3]
For the DNA Screen Investigator Group†

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2 Royal Melbourne Hospital, Melbourne, VIC.
3 University of Melbourne, Melbourne, VIC.

*Equal first authors.

†DNA Screen

In adult-onset genomic conditions, such as hereditary breast and ovarian cancer (HBOC), Lynch syndrome and familial hypercholesterolaemia, certain DNA variants confer high risk of developing future disease.[1] DNA screening for these conditions could thereby identify medically actionable genetic risk factors, prompting timely risk management and informed decision making from early adulthood to facilitate early detection or prevention.[2] Despite this opportunity, diagnostic rates for these conditions remain low,[2-4] limited by restricted access to genetic testing and lack of awareness.

Collectively, HBOC, Lynch syndrome and familial hypercholesterolaemia affect about
or 1.3% of the general population.[1] T
Centers for Disease Control and Pre
recently supported population DNA
for these conditions (given they mee
population screening), stating that t
would have "significant potential fo
on public health based on available
guidelines and recommendations"[5]

DNA screening for these conditions i
would augment existing population-
programs, such as BreastScreen and t
Cancer Screening Program, following
and principles outlined in the National Population Based Screening Framework.[7] DNA screening would

low public awareness of availability. A reliance on self-funded testing increases health inequalities. A criteria-free, population-based approach to genetic testing — population DNA screening using low cost testing for prevention in healthy adults — has the potential to identify far more people at high risk for these conditions. Population DNA screening would also identify high risk individuals earlier, enabling

detection rates are even lower, with an estimated > 95% of Lynch syndrome[14] and > 90% of familial hypercholesterolaemia high risk individuals

Box 1. **Wilson and Jungner classic screening criteria**[1]

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Box 2. **Synthesis of emerging screening criteria proposed over the past 40 years**

- The screening programme should respond to a recognized need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening programme effectiveness.
- The programme should integrate education, testing, clinical services and programme management.
- There should be quality assurance, with mechanisms to minimize potential risks of screening.
- The programme should ensure informed choice, confidentiality and respect for autonomy.
- The programme should promote equity and access to screening for the entire target population.
- Programme evaluation should be planned from the outset.
- The overall benefits of screening should outweigh the harm.

1. The condition sought should be an important health problem.

In adult-onset genomic conditions, such as hereditary breast and ovarian cancer (HBOC), Lynch syndrome and familial hypercholesterolaemia, certain DNA variants confer high risk of developing future disease.[1] DNA screening for these conditions could thereby identify medically actionable genetic risk factors, prompting timely risk management and informed decision making from early adulthood to facilitate early detection or prevention.[2] Despite this opportunity, diagnostic rates for these conditions remain low,[2-4] limited by restricted access to genetic testing and lack of awareness.

Collectively, HBOC, Lynch syndrome and familial hypercholesterolaemia affect about one in 75 people or 1.3% of the general population.[1] The United States Centers for Disease Control and Prevention (CDC) recently supported population DNA screening for these conditions (given they meet criteria for population screening), stating that this new approach would have "significant potential for positive impact on public health based on available evidence-based guidelines and recommendations"[5] (Box).

Medically actionable adult-onset genomic conditions[6]

Hereditary breast and ovarian cancer: high risk for breast, ovarian and prostate cancers due to DNA changes in genes that include *BRCA1*, *BRCA2* and *PALB2*[3]

Lynch syndrome: high risk for colorectal, endometrial, ovarian and other cancers due to DNA changes in genes that include *MLH*, *MSH2* and *MSH6*[4]

Familial hypercholesterolaemia: increased risk for coronary heart disease due to DNA changes in genes that include *LDLR*, *APOB* and *PCSK9*, causing very high cholesterol levels from an early age[6]

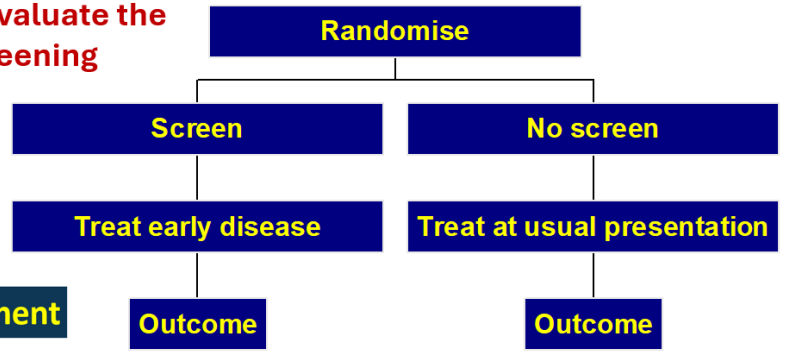
DNA screening for these conditions in Australia would augment existing population-based screening programs, such as BreastScreen and the National Bowel Cancer Screening Program, following the guidelines and principles outlined in the National Population Based Screening Framework.[7] DNA screening would identify younger high risk individuals based on genetic predisposition, optimally before the onset of any disease. These individuals would be managed separately from individuals with early stage cancers or disease precursors identified by other screening programs.

For HBOC, women at high risk are recommended to access regular breast surveillance (mammography, magnetic resonance imaging and/or ultrasound, as clinically indicated) and the option of risk-reducing mastectomy, to reduce breast cancer risk by at least 90–95%.[8] For ovarian cancer, although no effective screening options are available, risk-reducing salpingo-oophorectomy can lower the risk by 80%.[9] Given the poor prognosis following ovarian cancer diagnosis, this procedure can be life-saving. The benefits of identifying HBOC extend to men for early detection and treatment of prostate and male breast cancer. For Lynch syndrome, risk-reduction measures for colorectal cancer include aspirin use and regular colonoscopy, which together can reduce the risk by 60%.[10] Hysterectomy will reduce the risk of endometrial cancer by 90%.[11] For familial hypercholesterolaemia, the risk of premature cardiovascular disease can be managed through statin use and other cholesterol-lowering agents[4] to reduce the risk of myocardial infarction by up to 76%.[12]

2. There should be an accepted treatment for patients with recognized disease.
- There should be scientific evidence of screening programme effectiveness.

Evaluation of Screening Interventions?

RCTs are the only valid way to evaluate the benefits and harms of screening



Screening = Test + Effective management

3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.

even more high risk individuals and encourage further surveillance throughout the family. Large pilot studies ($N > 10\,000$ screened participants) are required to address questions relating to ethical and implementation issues, such as informed consent, access to genetic counselling, and clinical management of asymptomatic, apparently high risk individuals without disease family history.

Despite the availability of interventions and the ability to identify risk with precision using genomic technology, most high risk individuals for HBOC, Lynch syndrome or familial hypercholesterolaemia remain unidentified.[4,13,14] The prevalence of adults with high risk DNA variants for these conditions (approximately 1.3%)[1] far exceeds the current detection rates via clinical genetic testing, suggesting new approaches are required to increase access to testing. In the absence of Australian data, current criteria-based *BRCA1* or *BRCA2* testing in the United Kingdom is estimated to miss 50–90% of high risk women.[13] Lynch syndrome and familial hypercholesterolaemia detection rates are even lower, with an estimated > 95% of Lynch syndrome[14] and > 90% of familial hypercholesterolaemia high risk individuals remaining unidentified. This is especially significant for younger adults, for whom the preventive potential of genomic testing is greatest. Publicly funded genomic testing for these conditions is currently available only to Australians with disease or family history meeting strict eligibility criteria.[4,14,15] Access to high quality private testing is limited, with high cost and low public awareness of availability. A reliance on self-funded testing increases health inequalities. A

5. There should be a suitable test or examination.
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9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Our previously published health economic modelling studies of DNA screening for HBOC, Lynch syndrome[20] and familial hypercholesterolaemia[21] provide a platform for the consideration of DNA screening in Australia. Compared with current rates of clinical DNA testing, our modelling estimated that population DNA screening for HBOC and Lynch syndrome in adults aged 18–25 years would prevent 2411 cancers and save 1270 lives. At $200 per test, savings in prevented cancer treatment outweighed DNA screening costs, projecting DNA screening to be cost-saving for the Australian public health system (for cancer genes alone). Our model on DNA screening for familial hypercholesterolaemia genes found similar results.[21] Our future modelling will assess the combined benefits and costs of screening for familial cancer genes and familial hypercholesterolaemia genes concurrently in the same test.

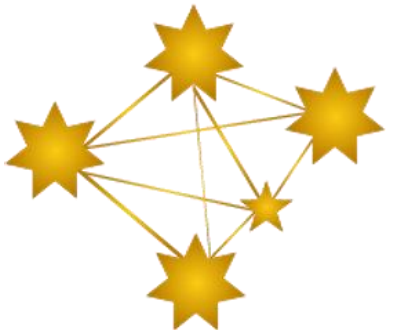
DNA Screen

POWERED BY M

Such a study will soon commence in Australia. The DNA Screen pilot study, designed by the DNA Screen Investigator Group and funded by the Medical Research Future Fund Genomics Health Futures Mission, will offer preventive DNA screening for HBOC, Lynch syndrome and familial hypercholesterolaemia to 10 000 Australians aged 18–40 years. The study will address current knowledge gaps in adult population-based DNA screening, and generate new evidence to inform future genetic screening in Australia. Recruitment will commence in mid-2022. DNA Screen will use innovative online recruitment methods, driven by social media, to ensure socially relevant communication for individuals aged 18–40 years. This age group will benefit most from preventive DNA screening, being old enough to provide informed consent but below the average age of disease onset and the commencement of existing Australian population-based screening programs. The pilot population recruited will be representative of the Australian general population in this age group, by state and territory population size, sex, with diverse cultural and linguistic representation, and Aboriginal and Torres Strait Islander participants. To achieve this, registered individuals will be randomly selected within categories for enrolment until 10 000 participants are recruited. The study will provide clear, video-enhanced information about genetic testing, risk management, implications of a positive and negative result, and other issues via the study website.

Results will be returned to participants using a national, evidence-based telehealth service, which has demonstrated acceptability in previous Australian studies.[18] Participants with high risk screening results (estimated to be approximately 133 individuals out of the 10 000 screened) will be contacted by telephone to explain the results and will be provided genetic counselling. Referrals will be made to relevant state-based clinical services in the public health care system for risk management, and for cascade testing of first degree blood relatives. The high risk genes being tested are incompletely penetrant, meaning not all individuals with high risk variants will develop the associated condition. Clinical services in each state have partnered with the study to ensure that onward management and appropriate downstream support are provided. Participants without high risk DNA changes (about 98% of participants) will be notified electronically, with links to further information provided about the testing conducted and meaning of the results, and access to genetic counselling if requested. After project completion, the primary outcomes (number of index cases, proportion eligible for reimbursed testing, and number of first degree blood relatives presenting for cascade testing) will be reported, and a cost-effectiveness analysis will be provided to the Australian Government for consideration of the possible development of a national adult DNA screening program.

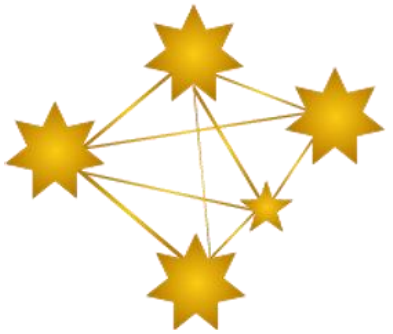
The Red Book – what does it say about genetic testing?



Routine population-based screening for genome-wide chromosome abnormalities and microdeletion syndromes is not recommended due to the absence of well-performed clinical validation studies.	**Not recommended (strong)**	N/A	3

https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/preventive-activities-in-general-practice/genetics/genetic-screening

The Red Book – Breast Cancer



Specific populations

For women at potentially high risk or carrying a mutation, offer referral to a familial cancer clinic for risk assessment, possible genetic testing and a risk reduction management plan.

Individualised surveillance and risk reduction plan, including consideration of associated risks for other cancers (eg ovarian), may include:

- regular clinical breast examination and annual breast imaging with mammography, MRI or ultrasound
- chemoprevention with selective oestrogen receptor modulators (SERMs; eg tamoxifen or raloxifene) or aromatase inhibitors (eg exemestane and anastrozole)[16]
- mastectomy and/or salpingo-oophorectomy.

https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/preventive-activities-in-general-practice/genetics/genetic-screening

The Red Book – Colorectal Cancer

Case finding

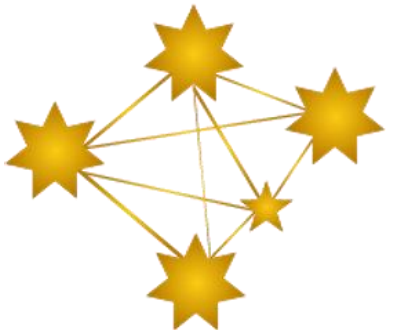
Recommendation	Grade	How often	References
For people at moderately increased risk of colorectal cancer: • colonoscopy should be offered every 5 years starting at 10 years younger than the earliest age of diagnosis of colorectal cancer in a first-degree relative or age 50 years, whichever is earlier, to age 74 years.	**Conditionally recommended**	Colonoscopy every 5 years	6
For people at potentially higher risk of colorectal cancer, where Lynch syndrome has been excluded: • colonoscopy should be offered every 5 years starting at 10 years younger than the earliest age of diagnosis of colorectal cancer in a first-degree relative or age 40 years, whichever is earlier, to age 74 years.	**Conditionally recommended**	Colonoscopy every 5 years	3

https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/preventive-activities-in-general-practice/genetics/genetic-screening

The Red Book Colorectal Cancer

Refer the following individuals to a clinical genetics service or familial cancer centre. **People with a personal history of colorectal cancer and any of the following features:** • isolated colorectal cancer diagnosed under age 50 years* • personal history of colorectal cancer and a second Lynch syndrome associated cancer (including two colorectal cancers) • personal history of colorectal cancer and a family history of one or more first-degree or second-degree relatives with colorectal or endometrial cancer, with at least one of the cancers diagnosed under age 50 years • personal history of colorectal cancer and a family history of two or more first-degree or second-degree relatives with a Lynch syndrome associated cancer,† regardless of the age the cancers were diagnosed. **People with a family history with any of these features:** • family history of two or more first-degree or second-degree relatives with colorectal or endometrial cancer, at least one of the cancers diagnosed under age 50 years • family history of three or more first-degree or second-degree relatives with a Lynch syndrome related cancer,† regardless of the age the cancers were diagnosed. *As some familial cancer services may have a lower referral age, please seek advice from your local genetics service. †Lynch syndrome–associated cancer includes adenocarcinoma of the colorectum, endometrium, small intestine, stomach, ovary, or pancreas, transitional cell carcinoma of the ureter or renal pelvis, cholangiocarcinoma, brain tumour, sebaceous gland tumours, keratoacanthoma.	**Conditionally recommended**	N/A	3,9

Resources



- eviQ, NSW Government - https://www.eviq.org.au/cancer-genetics/resources/3751-guide-for-health-professionals-ordering-genet
- The Red Book, RACGP - https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/preventive-activities-in-general-practice/about-the-red-book

Welcome Guest Panellist

Herman Professor of Primary Care Cancer Research,

Director of PC4, Victorian Comprehensive Cancer Centre (VCCC) Primary Care Research and Education Lead, NHMRC Leadership Fellow

Centre for Cancer Research, University of Melbourne

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Current Projects

Feasibility and acceptability of the co-designed e-HANDI for prescribing non-drug interventions in general practice: A before-after pilot trial

- The Institute for Evidence-Based Healthcare at Bond University invites GPs to participate in a pilot trial to understand the feasibility and acceptability of the recently co-designed “e-HANDI” (Handbook of Non-Drug Interventions) for prescribing NDIs at point of care.
- Results from this study will assist us in understanding the enablers and barriers to using NDI and HANDI in general practice and assist us in developing and co-designing a platform to ease the prescription of NDIs.
- This study will be undertaken over a 6-month period. All training will be provided. You will receive a gift card and be eligible for RACGP CPD points for your participation.

Scan the QR code for more

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Current Projects

Cancer Survivorship Care in General practice – a national survey

This study aims to assess GP and GP trainee comfort with providing cancer survivorship care in adult cancer survivors.

The survey has been developed by a team of Australian and international GPs together with allied health and nursing researchers, including A/Prof Joel Rhee, A/Prof Kylie Vuong, and Dr Elysia Thornton-Benko.

The survey should take no more than 12-15 minutes to complete. All participants are offered the chance to win one of three $100 gift vouchers of their choice. You can withdraw at any time without penalty and the survey is completely anonymous.

Scan the QR code for more

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