Cancer Genetics Group

NHS
UK Genetic Testing Network

Cancer Panels Workshop

8th May 2017

Chilworth Manor, Southampton

Cancer Genetics Group

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UK Genetic Testing Network

Breast cancer panel: genes for discussion

ATM

Breast cancer panel

ATM – reasons to include

- Significant role in cell cycle and dsDNA repair
- Confirmed moderate breast cancer risk for heterozygotes (RR2-4) in multiple studies; most significant in under 50s and account for 1-2% of cases on panels
  - (Tavera-Tapia et al 2017, Eliade et al 2017, Couch et al 2017, van Os et al 2016, Susswein et al 2016, Easton et al 2015, Maxwell et al 2015)
- Rare evolutionarily unlikely missense substitutions (dominant negative mutations) that confer increased risk similar to or greater than that of truncating mutations
- Specific variants confer more significant increased breast cancer risk (c.7217T>G), similar to that of BRCA2
  - (Stankovic et al 1998, Bernstein et al 2006, Tavtigian et al 2009, Goldgar et al 2011, Southey et al 2016)
- Potential for tailoring of treatment (PARP inhibitors)

Breast cancer panel

ATM – management proposals

- As per AT society NHS England approved guidelines, and in line with moderate/raised risk breast screening: annual mammography from 40-50 and national breast screening mammography from 50 years
- Specific variants/family history may be offered MRI
- Reproductive counselling

Breast cancer panel

ATM – reasons not to include

Clinical utility

- Is the variant the definitive explanation for the family history?
- Impact of test in care pathway for condition.
  - Surveillance.
  - Predictive testing.
- Potential for misinformation.

Breast cancer panel

ATM – reasons not to include

Informed consent for genetic testing :

- Requires Information on the specific gene or gene mutations being tested, including a description of the associated cancers and other potential health risks.
- "Informed" means that the person has enough information to make an educated decision about testing.

BARD1

Breast cancer panel

BARD1 – reasons to include

- Couch FJ. JAMA Oncol 2017. Case-control. 65,057 cases. OR 2.16 (95% CI 1.31-3.63)
- Buys, SS. Cancer 2017. Observational. N=35,409. 2% pathogenic mutations (3.3% in TNT)
- Ovarian studies underpowered, but positive reports - Walsh T. Proc Natl Acad Sci USA 2011; Norquist BM. JAMA Oncol 2016
- Neuroblastoma and other associations reported (Overview: Irminger-Finger, I. 2016)

Breast cancer panel

BARD1 – management proposals

- Management as per NICE guidelines for moderate risk of breast cancer for carriers
- Advise carriers of other possible cancer risks, but no additional screening/prevention
- No additional screening/prevention for negative predictive tested cases, unless proven breast/ovary phenocopy in family (assumes panel test performed in affected proband and/or consultand and no other high/moderate risk variant identified)

Breast cancer panel

BARD1 – reasons not to include

- Association with breast cancer but level of risk unclear (~0.5%-3% of cases)
  - RR 1.6 – 2.2. (Li et al, 2016, Couch et al 2017); conflicting findings re Cys557Ser mutation, but likely moderate risk gene
- Segregation analysis study in kConFab families did not confirm moderate risk gene (wide CI) [Li et al 2016]
- No LOH in breast cancer / non segregation in another breast ca in family (DeLeonardis et al 2017)

Breast cancer panel

BARD1 – reasons not to include

- Clinical utility unclear
  - Negative predictive test would not currently give sufficient reassurance to stop screening / danger of false reassurance to patient
  - Positive test does not lead to change in management, unlikely to justify additional screening by MRI or surgery, but may be misinterpreted
  - Potential in future for use in combination with other genes / possible treatment implications

BRIP1

Breast cancer panel

BRIP1 – reasons to include

- FANCJ gene, involved in DNA repair via homologous recombination
- Seal et al (2006) – RR for BrCa 2.0 (95% CI = 1.2-3.2, p = 0.012)

Breast cancer panel

BRIP1 – management proposals

- Moderate risk
  - Annual mammography 40-50
  - Consider chemoprevention

Breast cancer panel

BRIP1 – reasons not to include

BRIEF COMMUNICATIONS

nature genetics

Truncating mutations in the Fanconi anemia J gene *BRIP1* are low-penetrance breast cancer susceptibility alleles

Sheila Seal[1], Deborah Thompson[2], Anthony Renwick[1], Anna Elliott[1], Patrick Kelly[1], Rita Barfoot[1], Tasnim Chagtai[1], Hiran Jayatilake[1], Munaza Ahmed[1], Katarina Spanova[1], Bernard North[1], Lesley McGuffog[2], D Gareth Evans[3], Diana Eccles[4], The Breast Cancer Susceptibility Collaboration (UK), Douglas F Easton[2], Michael R Stratton[1,5] & Nazneen Rahman[1]

boundaries of *BRIP1* by conformation-sensitive gel electrophoresis (CSGE) in genomic DNA from 1,212 women with breast cancer and 2,081 controls (**Supplementary Methods** and **Supplementary Table 1** online). All the individuals with breast cancer had a family history of at least one first-degree relative with breast cancer or equivalent and/or a relative with ovarian cancer. Additionally, all affected individuals were negative for mutations and large deletions or duplications of *BRCA1* and *BRCA2* (see **Supplementary Methods** for full description of case and control series and mutational analyses of *BRCA1*, *BRCA2* and *BRIP1*). The use of this familial case-control design increases the power substantially[1].

We identified five different truncating mutations in nine of the 1,212 individuals with breast cancer, compared with two truncating mutations in the 2,081 controls ($P = 0.0030$; **Table 1** and **Fig. 1**).

This publication from 2006 is the only case-control study to provide evidence that *BRIP1* is a breast cancer predisposition gene

J Hum Genet. 2008;53(7):579-91. doi: 10.1007/s10038-008-0285-z. Epub 2008 Apr 15.

Mutational analysis of the breast cancer susceptibility gene BRIP1 /BACH1/FANCJ in high-risk non-BRCA1/BRCA2 breast cancer families.

Guénard F[1], Labrie Y, Ouellette G, Joly Beauparlant C, Simard J, Durocher F; INHERIT BRCAs.

Breast cancer panel

BRIP1 – reasons not to include

Association between **BRIP1** (BACH1) polymorphisms and **breast cancer risk**: a meta-analysis.

Pabalan N, Jarjanazi H, Ozcelik H.

Breast Cancer Res Treat. 2013 Jan;137(2):553-8. doi: 10.1007/s10549-012-2364-2. Epub 2012 Dec 6.

No evidence that protein truncating variants in **BRIP1** are associated with **breast cancer risk**: implications for gene panel testing.

Easton DF, Lesueur F, Decker B, Michailidou K, Li J, Allen J, Luccarini C, Pooley KA, Shah M, Bolla MK, Wang Q, Dennis J, Ahmad J, Thompson ER, Damiola F, Pertesi M, Voegele C, Mebirouk N, Robinot N, Durand G, Forey N, Luben RN, Ahmed S, Aittomäki K, Anton-Culver H, Arndt V; Australian Ovarian **Cancer** Study Group., Baynes C, Beckman MW, Benitez J, Van Den Berg D, Blot WJ, Bogdanova NV, Bojesen SE, Brenner H, Chang-Claude J, Chia KS, Choi JY, Conroy DM, Cox A, Cross SS, Czene K, Darabi H, Devilee P, Eriksson M, Fasching PA, Figueroa J, Flyger H, Fostira F, García-Closas M, Giles GG, Glendon G, González-Neira A, Guénel P, Haiman CA, Hall P, Hart SN, Hartman M, Hooning MJ, Hsiung CN, Ito H, Jakubowska A, James PA, John EM, Johnson N, Jones M, Kabisch M, Kang D; kConFab Investigators., Kosma VM, Kristensen V, Lambrechts D, Li N; Lifepool Investigators., Lindblom A, Long J, Lophatananon A, Lubinski J, Mannermaa A, Manoukian S, Margolin S, Matsuo K, Meindl A, Mitchell G, Muir K; NBCS Investigators., Nevelsteen I, van den Ouweland A, Peterlongo P, Phuah SY, Pylkäs K, Rowley SM, Sangrajrang S, Schmutzler RK, Shen CY, Shu XO, Southey MC, Surowy H, Swerdlow A, Teo SH, Tollenaar RA, Tomlinson I, Torres D, Truong T, Vachon C, Verhoef S, Wong-Brown M, Zheng W, Zheng Y, Nevanlinna H, Scott RJ, Andrulis IL, Wu AH, Hopper JL, Couch FJ, Winqvist R, Burwinkel B, Sawyer EJ, Schmidt MK, Rudolph A, Dörk T, Brauch H, Hamann U, Neuhausen SL, Milne RL, Fletcher O, Pharoah PD, Campbell IG, Dunning AM, Le Calvez-Kelm F, Goldgar DE, Tavtigian SV, Chenevix-Trench G.

J Med Genet. 2016 May;53(5):298-309. doi: 10.1136/jmedgenet-2015-103529. Epub 2016 Feb 26.

Associations Between **Cancer** Predisposition Testing Panel Genes and **Breast Cancer**.

Couch FJ, Shimelis H, Hu C, Hart SN, Polley EC, Na J, Hallberg E, Moore R, Thomas A, Lilyquist J, Feng B, McFarland R, Pesaran T, Huether R, LaDuca H, Chao EC, Goldgar DE, Dolinsky JS.

JAMA Oncol. 2017 Apr 13. doi: 10.1001/jamaoncol.2017.0424. [Epub ahead of print]

CDH1

Breast cancer panel

CDH1 – reasons to include

Recommendations of who to test (Fitzgerald et al 2015) include

- Families with Diffuse gastric cancer and lobular breast cancer (one diagnosis under 50)
- To be considered in bilateral or familial lobular breast cancer before age 50
- Often pathology data may be unavailable in historic cases

- **Small families may mean individual gene testing criteria are not met**
  - Rosenthal et al 2017-

    9,751 pathogenic variants in the selected breast cancer risk genes were identified in 9,641 women.

    BRCA1/2 accounted for 59.1% of the pathogenic variants and 38.8% were in ATM, CHEK2, or PALB2.

    Only 24.7% of all women with pathogenic variants found in any gene reached >20% lifetime risk threshold using the Claus model.
- **Rare high risk gene**
  - CDH1 is Included as a high-risk breast cancer gene in many panels/studies in recent literature with TP53, PTEN and STK11
  - Corsa et al 2016
    - 428 LBC families screened for CDH1- 2.9% deleterious mutations
  - Schrader et al 2011
    - In a study of 318 women who had a personal and family history of LBC but no family history of DGC, 1.3% had a ***CDH1*** germline pathogenic variant.
- **High risk breast cancer gene**
  - excluding missense mutations and using data derived from highly ascertained families. (Likely to be lower if ascertained via panel testing)
    - Risk of lobular breast cancer 42% for mutation carriers
    - Diffuse Gastric Cancer by age 80: men 70%, women 56%
    - Li et al 2016 – found 31 putative deleterious mutations in 7 known breast cancer susceptibility genes (TP53, PALB2, ATM, CHEK2, CDH1, PTEN and STK11) in 45 cases, and 22 potential deleterious mutations in 31 cases in 8 other genes (BARD1, BRIP1, MRE11, NBN, RAD50, RAD51C, RAD51D and CDK4). The relevant variants were then genotyped in 558 family members. Assuming a constant relative risk of breast cancer across age groups, **only variants in CDH1,** CHEK2, PALB2 and TP53 **showed evidence of a significantly increased risk of breast cancer,** with some supportive evidence that mutations in ATM confer moderate risk.
- **Actionable implications linked to detection of a truncating mutation**

Breast cancer panel

CHD1 – management proposals

- **Pathogenic mutation detection**
  - Consider prophylactic gastrectomy from age 20-30
  - Regular endoscopy and biopsy (HDGC protocol in specialist centre) if gastrectomy deferred
  - Breast awareness/annual clinical breast exam
  - MRI screening from age 30
    - Mammography screening sensitivity low (34-92%) in lobular breast cancer
    - (Ultrasound better for LBC than mammography)
  - Breast cancer chemoprevention
  - RRM consider on a case-by-case basis taking into account the family history
  - Consider colonoscopy in families where CRC has occurred

Breast cancer panel

CDH1 – reasons not to include

1. Relevant to lobular only
2. Penetrance remains unclear – likely to be seriously affected by ascertainment bias
3. VUS and large deletions

INVITED COMMENTARY | Genetics inMedicine

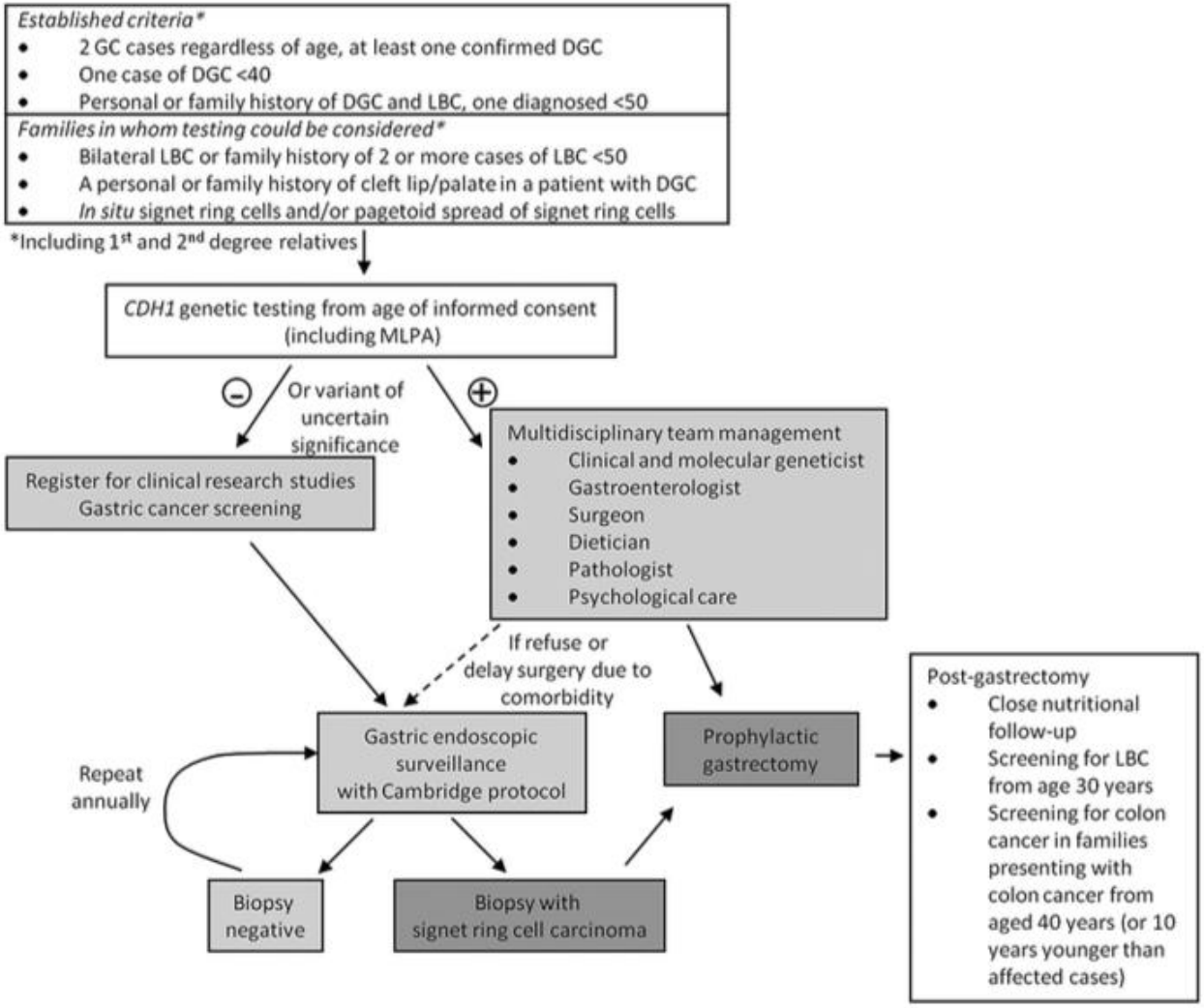
CDH1 germline mutations: different syndromes, same management?

Patrick R. Benusiglio, MD, PhD

Just over 20 years ago, Gorlin *et al.* introduced a new medical entity, the blepharocheilodontic syndrome (BCD).[1] Its initial features were ectropion of the lower eyelids; eurvblepharon

cancer (DGC) and invasive lobular carcinoma of the breast (ILC), two cancers that invariably show somatic inactivation of E-cadherin or one of its partners. Multiple cases of DGC

4. Guidelines already exist



CHEK2

Breast cancer panel

CHEK2 – reasons to include

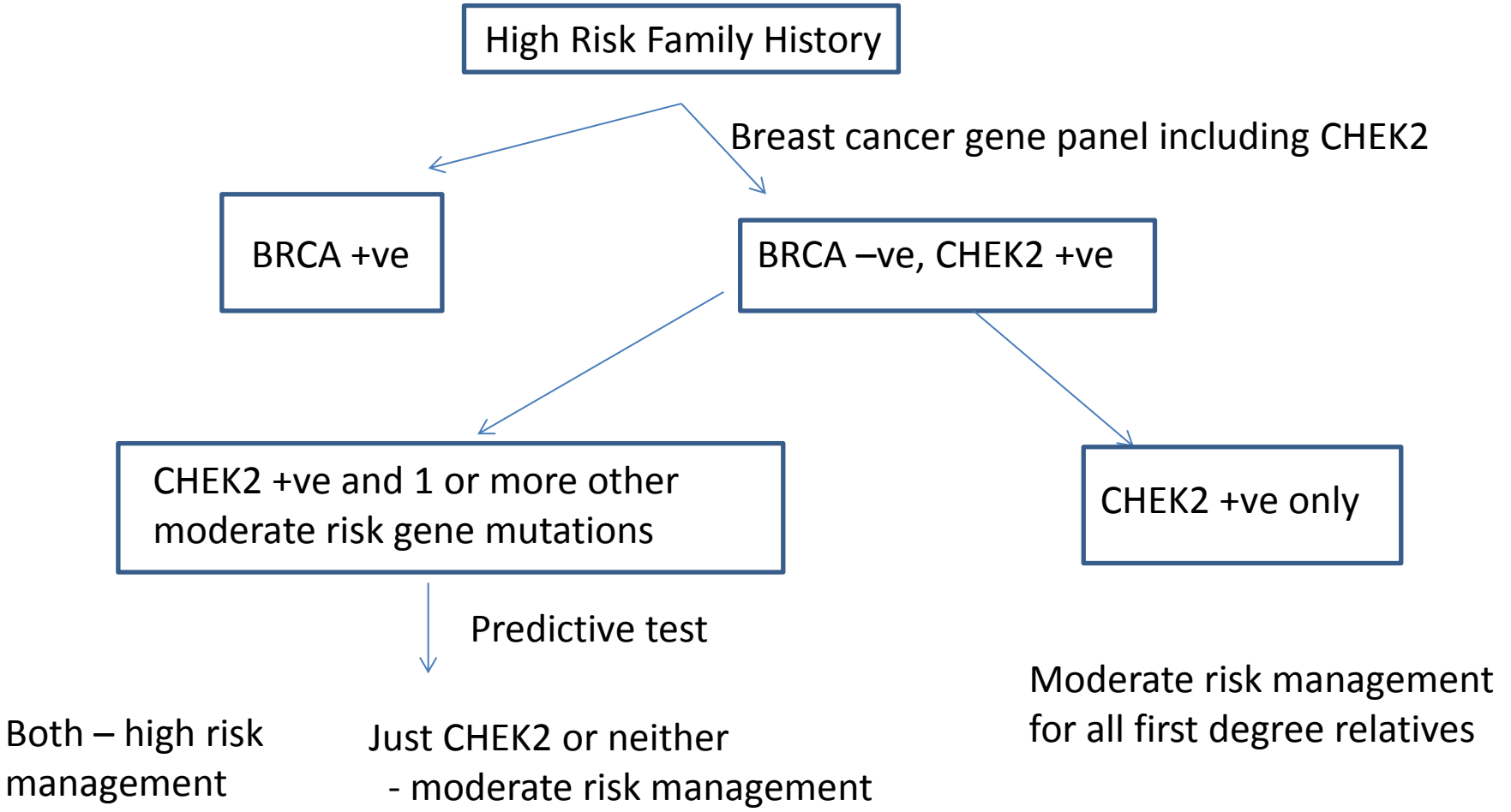
- Well defined moderate risk breast cancer gene, particularly for the common CHEK2*1100delC mutation (caucasian populations)
- Confers a 2-3 fold increase in risk with a lifetime breast cancer risk reported from 22 -37%
- CHEK2*1100delC carriers have a higher risk of developing bilateral breast cancer
- It is not uncommon to identify more than 1 mutated moderate risk breast cancer gene in a patient with a strong family history - conferring a high risk

- The same genetic modifiers for the BRCA genes as assessed by the polygenic risk score (PRS – based on 77 low penetrance variants) affect the risk associated with CHEK2
- Study by Muranen et al
  - 20% CHEK2*1100delC carriers with high PRS score had a lifetime risk of 32.6% - high risk
  - 20% CHEK2*1100delC carriers with low PRS score had a lifetime risk of 14.3% - low risk
- By only testing high risk families we enrich for families with a high PRS score

So, diagnostic testing for “moderate “ risk cancer genes can provide an explanation for a family history and in some cases can identify a high risk

Breast cancer panel

CHEK2 – management proposals



Breast cancer panel

CHEK2 – reasons not to include

- Variants do not segregate with disease
  - E.g. Vahteristo *et al*, 2001 & Meijers-Heijboer *et al*, 2003
- Lifetime risk of developing breast Ca
  - 25% if strong family history
  - ?large enough to warrant risk reducing surgery
- Impact on management
  - Identification of LoF variant would confer moderate risk
  - But already only testing patients already established as at least moderate risk from family history
  - Would such a result impact on screening?
  - Need to be cautious as negative testing in mutation positive families could give false reassurance of lower risk

Conclusions

- Interpretation of impact of variants other than c.1100delC difficult
- Single mutation test (c.1100delC) in presence of strong family history may identify higher risk individuals but negative test may give false reassurance of lower risk.
- CHEK2 testing may be more informative as part of a polygenic test rather than stand alone test in the future.

NBN

Breast cancer panel

NBN – reasons to include

Reported as a moderate risk gene in Poland due to a known Founder mutation

NBN 657del5, associated with a 3.13 RR breast cancer (Steffen J, 2006) and RR 2.7 (1.9-3.7 90% CI)[Tung 2016]

Moderate breast cancer risk is similar to ATM.

Therefore would be most relevant to the Polish population in UK

It has been included on many extended breast cancer multigene panels including Ambry Genetics, Blueprint Genetics, Leeds cancer gene panel & Trusight

In a recent German study by Kraus et. al, 6 NBN mutations were identified in 6 patients with breast cancer and a positive brca family history, out of 105 patients with mutations in a cohort of 588 breast and ovarian cancer patients meeting hereditary testing guidelines.

Int J Cancer. 2017 Jan 1;140(1):95-102. doi: 10.1002/ijc.30428. Epub 2016 Sep 23. Gene panel sequencing in familial breast/ovarian cancer patients identifies multiple novel mutations also in genes others than BRCA1/2.

The most recent largest cohort panel gene testing analysis from AMBRY reported in April 2017

Associations Between Cancer Predisposition Testing Panel Genes and Breast Cancer

Fergus J. Couch, PhD; *JAMA Oncol.* Published online April 13, 2017. doi:10.1001/jamaoncol.2017.034

Study was of 38326 women, 2012-2016 tested on multigene panels

Identified 5 genes that did not confer increased breast cancer risk in this analysis and need further study: *BRIP1, NBN, MRE11A, RAD50, RAD51C*

Even larger numbers are required to confirm or refute a possible effect, hence the reason for inclusion, as NBN mutations are rare, so data is limited, but will increase with more panel test outcomes

Breast cancer panel

NBN – management proposals

- Many papers cite a moderate breast cancer risk, based on small case-control studies RR 2.7
- Therefore management guidelines would include moderate risk screening as a minimum, annual mammography from 40-49, but not MRI
- High risk surveillance (annual mammograms 40-59) would only be advised if there were multiple cases of early onset breast cancer
- RRM would not be advised as lifetime brca risk is unlikely to reach >30%

Breast cancer panel

NBN – reasons not to include

- Data for breast cancer risk is limited / poorly defined
- Multiple polymorphisms/population dependant
- Data applies only to one specific mutation within one population e.g. 657del5 (Poland)
- Recent papers focussing on multi-gene panel testing have shown no evidence to include
- **Li *et el* 2016 Targeted massively parallel sequencing of a panel of putative breast cancer susceptibility genes in a large cohort of multiple-case breast and ovarian cancer families. J Med Genet**
  - 684 'non-*BRCA1/2*' families (kConFab) tested for 17 known/putative breast cancer susceptibility genes. Concluded that risk estimates too imprecise to describe as high or moderate risk
- **Couch et al 2017 Associations Between Cancer Predisposition Testing Panel Genes and Breast Cancer JAMA Oncol**
  - 65 057 patients with breast cancer tested with multigene panels. Concluded that NBN not associated with increased breast cancer risk

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Ovarian cancer panel: genes for discussion

BRIP1

Ovarian cancer panel

BRIP1 – reasons to include

- Case control studies –deleterious mutn present in 0.92% cases of EOC compared to 0.09% controls
- Relative risk of invasive EOC ~11
- UKFOCSS 0.6% compared to controls
- Lifetime risk 5.8% estimated- Moderate risk

Ovarian cancer panel

BRIP1 – management proposals

- Later onset EOC- (~64y)- consider post menopausal BSO
- Targeted therapies eg PARP / cisplatin may be possible
- No increase in Breast Cancer risk - NHSBSP

Ovarian cancer panel

BRIP1 – reasons not to include

- First do no harm
- (respect the hard-won scientific gains…, and share such knowledge, etc.)
- Clinical utility requires knowledge:
  1. reason/explanation for cancer
  2. Future risk to mutation carrier
  3. Management
  4. Risk to *non*-mutation carrier in the same family

Ovarian cancer panel

BRIP1 – reasons not to include

- Reason/explanation for cancer
  - 10x more common in cases than control (0.92% vs 0.09%), *older.*
- Risk to mutation carrier
  - **RR 11.22** (CI 3.22-34)- non family-based study
  - **RR 3.41**(2.12-5.54)-included UKFOCSS, enriched for genetic/ env modifiers
  - **Cumulative risk to age 80y 5.8%** (3.6-9.1)
  - No good evidence of significantly increased risk of breast cancer
- Management
  - BSO at 5.8% risk?
  - PARPi benefit- hypothetical (ARIEL2 study not encouraging)
- Risk to non-mutation carrier in the same family
  - ?

Refs: Ramus at al JNCI (2015); 107 (11); Balmana and Domchek JCNI (2015 107 (11); McNeish et al J Clin Oncol (2015);33

EPCAM (del exons 8-9)

Ovarian cancer panel

EPCAM – reasons to include

- Extra-colonic manifestations have been seen
- But little is described in the literature about ovarian cancer – seems to be uncommon
- Kempers et al. Lancet Oncol2011 – no ovarian cancers!
- Tumours are confined to tissues which express EPCAM – mosaic inactivation of MSH2
- EPCAM is expressed in ovarian tissue
- Establish the risk – confirm the rarity/absence of mutations

Ovarian cancer panel

EPCAM – management proposals

- Conservative unless data accumulates that there is a significant risk

Ovarian cancer panel

EPCAM – reasons not to include

- 1-3% Lynch syndrome reported to be caused by deletion of two exons of EPCAM
- Risk of OVCA in del EPCAM reported to be 4-12%
  - overlap with general population risk of OVCA)
- Reports from small series with poor detail of case selection
  - e.g. 56 “Lynch patient from Poland- 7% del EPCAM
- Kraus: 6/581 del variant but 89 had a VUS

- Population attributable risk of del EPCAM not reported

Ovarian cancer panel

EPCAM – reasons not to include

- If Lynch syndrome 1 in 440
- 2% of this is EPCAM
  - 1 in (440 x 50) = 1 in 22000- and much of this will not be OVCA…

- What proportion of OVCA is EPCAM????
- How good is deletion test in panel- do we need to do MLPA as well??

- I would test more people for BRCA1 &2 rather than test OVCA for EPCAM
- If the family history suggests Lynch then do IHC / MSI in best person to direct the genetic analysis- and that will help you to interpret your variants

STK11

Ovarian cancer panel

STK11 – reasons to include

- *STK11* mutations are associated with Peutz-Jeghers Syndrome (PJS) which is chiefly characterized by the association of gastrointestinal polyposis and mucocutaneous pigmentation.
- PJS patients have 21% risk of OvCa (c/w 1.6% in gen pop) with an average age of diagnosis of 28 years old. Mostly sex cord tumors with annular tubules (SCTATs) and mucinous tumors of the ovaries and fallopian tubes. Source: GeneReviews.
- Loss of juvenile freckling. PJS may not be clinically apparent until 2nd or 3rd decade of life. Variable presentation/expressivity. Thus OvCa may present before colonic symptoms. Source: Medscape.
- 17-40% may have no apparent family history (?*de novo* rate vs variable familial presentation). Source: GeneReviews.
- Data from >95,000 women screened via Myriad 25 gene hereditary cancer panel: 11 genes showed significant assoc with OvCa by multivariate regression. *STK11* had an OR of 41.9 (highest of all genes tested). Source: Kurian et al. ASCO 2016 abstract 5510.

Ovarian cancer panel

STK11 – management proposals

- Treatment/surveillance:

  Pelvic exam, smear test & transvaginal ultrasound (from age 18) to monitor ovaries, cervix & uterus. Sources GeneReviews & NCCN guidelines.

- Query: risk reducing surgery appropriate for breast/ovary/uterus?
- Relatives: Presymptomatic/familial mutation testing.

- Marc will discuss management of *STK11* patients in his talk later today.

Ovarian cancer panel

STK11 – reasons not to include

- Majority of ovarian cancer is of high grade serous histology, epithelial origin, presenting at advanced stage
- Primary mucinous carcinomas of epithelial origin and non-epithelial sex cord stromal tumours of ovary are relatively uncommon
- Different histological types have distinct pathways of development
- Ovarian panel most likely to be offered in breast/ovarian families or families with 2 or more ovarian cancer diagnoses
- In these families ovarian cancer will be of epithelial origin with serous/endometroid/clear cell histology in the vast majority of cases
- PJS typically associated with ovarian sex cord tumours with annular tubules and other non-epithelial tumours
  - Reports of association with mucinous and borderline epithelial ovarian tumours
  - No reports of association with high-grade serous/endometrioid/clear cell ovarian cancer

Ovarian cancer panel

STK11 – reasons not to include

- Van Lier *et al* Am J Gastroenterol 2010
  - Dutch series of 69 females with PJS – 2 malignant Sertoli cell, 1 ovarian small cell cancer
- Resta *et al* Dig Liver Dis 2013
  - Italian series of 61 females with PJS, 3 had ovarian cancer – 1 was malignant SCTAT, other 2 histology not reported
- Minion *et al* Gyn Oncol 2015
  - 911 BRCA-negative probands with PH breast and/or ovarian cancer - 466 ovarian cancer patients – 19 gene panel – no mutations in STK11
- Kurian *et al* J Clin Oncol 2016
  - 95,561 women tested with 25 gene panel – examined association between pathogenic variants and personal history of ovarian cancer (5,020 cases) – STK11 41.9 OR (CI 5.55, 319) whereas BRCA1 11.8 and BRCA2 5.26
  - Histology of the ovarian cancers associated with STK11 mutations not reported
  - Authors agreed the STK11 result was an outlier and requires further study

TP53

Ovarian cancer panel

TP53 – reasons to include

- We know TP53 is a cancer susceptibility gene but its significance in inherited ovarian cancer and the interpretation of variants is unclear
- If we want to move beyond simple panels to true genomics we need to take a 'jump into the unknown' and build expertise
- Including this known cancer susceptibility gene in new panels and developing internationally accessible databases is the way to drive forward our understanding but we must define result feedback mechanisms together before consent takes place

Ovarian cancer panel

TP53 – management proposals

- Consent pre-testing needs to be clear and agreed: including what we will report back

- I would only recommend BSO as part of a wider planned gynaecological operation if also keen to lower oestrogen load to combat familial breast cancer risk
- Dr Julian Barwell

Ovarian cancer panel

TP53 – reasons not to include

- Ovarian cancer is not a common phenotype in individuals with germline *TP53* mutations

(for evidence see: Villani et al. Lancet Oncol. 2016 Sep;17(9):1295-305, Arcand et al. BMC Med Genet. 2015 Apr 12;16:24. Giacomazzi et al. Cancer. 2013 Dec 15;119(24):4341-9, Ruis *et al*. J Med Genet. 2010 Jun;47(6):421-8, Gonzalez *et al*. J Clin Oncol. 2009 Mar 10;27(8):1250-6, Nichols et al. Cancer Epidemiol Biomarkers Prev. 2001 Feb;10(2):83-7, Birch et al. Cancer Res. 1994 Mar 1;54(5):1298-304., Garber et al. Cancer Res. 1991 Nov 15;51(22):6094-7 etc.)

- If we include *TP53* on an ovarian cancer panel, could we equally argue the need to sequence this gene in every cancer type ever seen in a pt with a germline *TP53* mutation?
  - Are we being equitable in access to testing?
- How are we defining the clinical criteria warranting an "ovarian cancer panel"?
  - Is a germline *TP53* mutation likely to explain the phenotype in OC only families?
  - How do we interpret the result in this context?
  - How do we interpret VUS?
- Are we going to offer prophylactic BSO to *TP53* carriers?
  - If not, why are we testing?

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Bowel cancer/polyposis panel: genes for discussion

GREM1 (upstream dup)

Bowel cancer/polyposis panel

Basic principles

- In an ideal world it would be lovely to test for everything we know about

but

- Resources are scarce – and likely to get more scarce
- UVs are common, particularly in genes that are not well known – and can take a lot of scientist and clinician time to interpret
- Need to target resources where most likely to find information that will alter management
- Equity c.f. other patients – currently offer BRCA testing if estimated 10% chance of mutation

Bowel cancer/polyposis panel

GREM1 (upstream dup) – reasons not to include

- Very rare and reports so far in specific population – Ashkenazi Jewish
- Technical – duplication – not covered by NGS panels such as Trusight
- More appropriate to arrange as specific test if panel negative +/- known appropriate ancestry

GREM1 – summary of literature

- Jaeger 2012 – Nat Genet – 6 AJ families + 1 (CORGI) – also AJ
- Laitman 2015 - 194 AJ with CRC FH – 1 mutation
- Lieberman 2017 (Israel) - 4 families

- Rohlin 2016 – 1 family – similar duplication (not seen in 107 cohort with CRC/polyposis)
- Venkatachalam 2011 – 41 pts with CRC <40 – 1 GREM1 whole gene dup inc ex 3-6 SCG5

Bowel cancer/polyposis panel

GREM1 (upstream dup) – reasons to include

- A gene, mutation(s) in which are known to have a clinically significant effect on CRC risk
  - If by 'gene' we mean 'functional unit' and not just coding region
- Accuracy of pathology/endoscopy reports; the histopathology of unusual polyps is frequently mis-reported, especially in mixed/JPS/PJS polyposis; genetic tests have superior specificity
  - Wallace MH, et al. (1999) Attenuated adenomatous polyposis coli: the role of ascertainment bias through failure to dye spray at colonoscopy. *Diseases of the Colon and Rectum* **42**:1078-80.
  - Frayling, IM, & Arends, MJ. (2015). How can histopathologists help clinical genetics in the investigation of suspected hereditary gastrointestinal cancer? *Diagnostic Histopathology* **21**(4):137-146.
  - Frayling IM. (2005) *Familial Adenomatous Polyposis ; Peutz-Jeghers Syndrome ; Juvenile Polyposis Syndrome,* in: Oxford Desk Reference - Clinical Genetics Eds: Firth HV, Hurst JA, consulting editor Hall JG. OUP.
- Just because an individual has a mutation in one gene does not preclude mutation/s in other gene/s
  - Whitworth J, et al. (2016) Multilocus Inherited Neoplasia Alleles Syndrome (MINAS): Case reports and literature review. *JAMA Oncology* **2**(3):1-7.

Bowel cancer/polyposis panel

GREM1 (upstream dup) – management proposals

- Expert advice on clinical management is available from rare disease specialists and reference centres, such as St Mark's in the UK, and *InSiGHT* on an international basis. "No one acts alone."
  - https://www.insight-group.org/
- The original Hereditary Mixed Polyposis Syndrome family with a *GREM1* upstream duplication is largely cared for by/known to St Marks, with input from Prof. Ian Tomlinson, so any further or similar UK cases should be reported to and discussed with them
  - UK Rare Disease Policy and NHS support for specialists in rare diseases
- The interpretation of other putative variants/mutations in/around *GREM1* is not a matter for individuals, but concerted teams on an international basis, e.g. InSiGHT, incl. Prof. Tomlinson.
  - As for MMR genes, as in current UK laboratory guidance [ACGS].

NTHL1

Bowel cancer/polyposis panel

NTHL1 – reasons not to include

Appears very rare (?more common in Dutch)

AR and polyposis phenotype

More appropriate to target test to appropriate families if panel negative

Bowel cancer/polyposis panel

NTHL1 – summary of literature

- Weren 2015 – exome seq 48 families (51 ind)

3 Dutch families (7 individuals) – homozygous for same truncating mutation

- Rivera 2015 – 1 patient – multiple tumours – compound heterozygote common mutation + splicing
- Broderick 2017 UK – reviewed sequence data from 863 familial CRC cases without mutations in common genes – one compound heterozygote – 41 year old man polyposis – common mutation + another truncating

- Zhang – 140 Chinese CRC <35 – no mutations
- Dallosso – 2008 – no significant variants in 167 patients with multiple colorectal adenomas and FH consistent with AR inheritance (UK)

Bowel cancer/polyposis panel

NTHL1 – reasons to include

- A gene, mutations in which are known to have a clinically significant effect on CRC risk
- Uncertainty as to the *NTHL1*-associated phenotype
- Accuracy of pathology/endoscopy reports and polyp counts; the histopathology of polyps is frequently mis-reported
  - Wallace MH, et al. (1999) Attenuated adenomatous polyposis coli: the role of ascertainment bias through failure to dye spray at colonoscopy. *Diseases of the Colon and Rectum* **42**:1078-80.
  - Frayling, IM, & Arends, MJ. (2015). How can histopathologists help clinical genetics in the investigation of suspected hereditary gastrointestinal cancer? *Diagnostic Histopathology* **21**(4):137-146.
- *NTHL1* mutations will explain a proportion of "LS-like syndrome" (LLS)
- Just because an individual has a mutation in one gene does not preclude mutation/s in other gene/s
  - Whitworth J, et al. (2016) Multilocus Inherited Neoplasia Alleles Syndrome (MINAS): Case reports and literature review. *JAMA Oncology* **2**(3):1-7.

Bowel cancer/polyposis panel

NTHL1 – management proposals

- Expert advice on clinical management is available from rare disease specialists and reference centres, such as St Mark's in the UK, and *InSiGHT* on an international basis. "No one acts alone."
  - https://www.insight-group.org/
- The precise phenotype associated with mutations in *NTHL1* may be unclear, but the spectrum of disease appears to be akin to a combination of *MUTYH*-associated polyposis and Lynch syndrome. Hence care can be based on existing guidance for MAP and LS, with prospective collection of data to inform review
  - Weren, R. D., et al. (2015). A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer. *Nature genetics*, **47**(6), 668-671.
  - UK Rare Disease Policy and NHS support for specialists in rare diseases
- The interpretation of other mutations in/around *NTHL1* is not a matter for individuals, but concerted teams on an international basis, i.e. *InSiGHT*.
  - As for MMR genes, as in current UK laboratory guidance [ACGS].