With well characterised bio-bank samples, the secret of aggressive prostate cancer is unlocked.

On behalf of the kConFab consortium: www.kconfab.org
kConFab history

Established in 1997, we are a biobank (cohort) with linked data, to facilitate breast, ovarian prostate & pancreatic cancer genetic research.

We obtain signed consent from participants at very high risk of breast and ovarian cancer via the 32 Family Cancer Clinics in Australia and New Zealand – BRCA1/2, PALB2, ATM, p53.

From all family members (females and males over 18 years, affected & unaffected) we collect germline mutation test reports, medical/treatment, lifestyle information and biological material such as tissue (normal and cancer) removed at surgery and blood. Routine annual follow up.

We verify all cancers diagnosed reported in a family, preferably with a pathology report.

On average 10 bloods and 5.2 cases of breast cancer/family – ideal for segregation studies to determine if a variant tracks with disease.

The biobank supplies to 162 projects world wide (1/3 active 15 hears) & 340 high ranking publications

The work - publications span basic biology, genetics – gene discovery, lifestyle factors, psychosocial and research for new treatment options based on a patients genetic profile.
A typical kConFab Family

9 diagnosed with breast cancer – 1 male breast cancer, 2 ovarian cancers and 2 prostate cancers.
Was there a genetic factor causing so many prostate cancers in multi-case breast cancer families?

Was its occurrence expected? as prostate cancer (PC) is also a common cancer. 

Or

Was the genetic fault that was causing breast cancer, BRCA1 or BRCA2, also causing the prostate cancer in these family members?

The association between a BRCA1 or BRCA2 mutation and prostate cancer through genetic analysis is of paramount importance in further understanding the risk of prostate cancer to men within these families and their treatment response, esp. in the era of personalised medicine.

By 2009, 1,423 families had been recruited to kConFab.

147 men diagnosed with PC and with a known pathogenic BRCA germline mutation status.

• 36 BRCA2 mutation carriers had FFPE tissue/blood available and comprehensive treatment details. The majority of these men (79%) were classified as High Risk using the D’Amico risk stratification:
  - Stage > T2c or
  - Gleason score ≥ 8 or
  - PSA level > 20 ng/mL

• 11 BRCA1 mutation carriers were eliminated from further analysis due to small numbers.
Study 1.

36 BRCA2 carriers treatment outcomes:
70% (5 yrs) ; 30% (10yrs) were deceased.
This is in contrast to High Risk men in general population: 94% at 5 yrs ; 80% alive at 10 yrs

Amongst our cohort:

a) 79% of BRCA2 mutation carriers had High Risk disease at diagnosis
b) 23/36 BRCA2 mutation carriers died with a mean survival of 3.5 years
c) A BRCA2 mutation status was a significant predictor of overall survival (HR= 3.175) and of prostate cancer related survival (HR=4.968).
d) Age adjusted serum PSA readings prior to diagnosis were elevated in 90% of men

From the review of treatment outcomes, a BRCA2 mutation is associated with aggressive prostate cancer with poor survival.
Study 2. Establishment of Primary PDX of *BRCA2* mutation carrier tumour specimens. Why are these tumours so aggressive?.

Collect and dissect fresh prostate tumour tissue n= 11 patients

4mm³ sized pieces grown under kidney capsule

8 weeks

Collect and analyze grafts. Xenografts faithfully retain the H&E pathology and *BRCA2* genetic alterations of original patient tumour. n = 100% take

*Know what you grow* as there are different prostate cancer pathologies: adenocarcinoma (is common) and can differentiate to Intra Ductal Carcinoma—Prostate (IDC-P) vs. ductal. Neuroendocrine is another pathology type

Importantly, the pathology in our *BRCA2* PDX was both adenocarcinoma with a large, over represented component of IDC-P. Due to the H&E and genomic QA, we were confident that PDX model retains the pathologies of patient *BRCA*-mutation carrier tumours.

IDC-P is historically considered a premalignant lesion and associated with:

- High-grade disease
- Large tumour volume
- Poor clinical outcomes

Significantly, not routinely reported by pathologists
Retrospective study using kConFab prostate cancer patients H&Es to determine frequency of IDC-P in BRCA2-carriers vs. sporadic PC cases

Archived H&E slides were reviewed by our uropathologist.

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<tr>
<th></th>
<th>Sporadic</th>
<th>BRCA2 carriers</th>
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<tbody>
<tr>
<td>n</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>IDC-P present</td>
<td>3 (9%)</td>
<td>14 (42%)</td>
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Importantly, not one clinical pathology report detailed the IDC-P morphology

Within the BRCA2 carrier group:
- 42% of BRCA2 carriers had IDCP, 58% did not.
- Multivariate analysis revealed that in BRCA2 patients with IDCP they had poor outcome in terms of time to survival.
Study 3. In addition to a germline \textit{BRCA2} mutations are there other driver mutations in prostate cancers?

Generated mutational profiles of \textit{BRCA2} carriers vs. 200 sporadic cases (Uni of Toronto).

- We used whole-genome sequencing (WGS), along with genotyping and methylation arrays, to fully characterize localized PCa.
- Localized \textit{BRCA2} carrier tumours show elevated genomic instability and a mutational profile that more closely resembles mCRPC than localized sporadic PCa.
- \textit{BRCA2} carriers PCa is defined by unique copy number gains and hypomethylation events. These include alterations in pathways associated with negative prognosis, including the \textit{MED12L}/\textit{MED12} axis, which are frequently dysregulated in mCRPC.
- IDC-P and adenocarcinoma are clonally-related but distinct lesions.
Conclusions:

Data and biospecimens from a small but well annotated patient cohort complements but is different to large scale studies such as the ICGC. A well characterised patient profile that includes germ-line mutation test results, pathology, all treatments, their outcomes and annual follow up has identified a sub-set men who are at for high risk prostate cancer.

Thorough QA at each step has identified important clinical features and the pathways involved in aggressive Pca that has a poor outcome.

Clinical impact:

- In many international centres now ask their Uropathologist to note the presence or absence of IDCP. This request has been approved at a recent international pathology consensus meeting.
- Alter standard care of BRCA 2 patients – immediate, multi-modal therapy, not active surveillance.
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