CASE STUDY: Research impact on prognostic models for patients with a Blood Cancer, MPN

E Joanna Baxter and the Cambridge Blood and Stem Cell Biobank team
NHS-BT Cambridge Centre, Long Road, Cambridge.

FURTHER INFORMATION AND TO CONTACT US:
www.haem.cam.ac.uk/Cambridge_Blood_and_Stem_Cell_Biobank
01223 588048
CBSB_admin@medschl.cam.ac.uk

The Cambridge Blood and Stem Cell Biobank (CBSB) is a sample processing lab combined with a research nurse team integrated into clinical service at Addenbrooke's and the Rosie Hospitals; Cambridge.

We support research investigating normal blood cell formation, stem cell function, normal aging of blood cells; and increase understanding of diseases of the blood and immune system. Many lead to potential treatments of these conditions.

Lead by Dr George Vassiliou (*Lead Clinician*), Dr Joanna Baxter (*Lead Scientist*) Professor Brian Huntly *(Director).*

CASE STUDY: ESTABLISHING A PERSONALISED PROGNOSTIC MODELS IN MPNs

INTRODUCTION:

- *MPNs are a group of chronic malignant disorders* with variable outcome; some cases develop leukaemia and others live a fairly normal life.
- *Three common mutations* are found in these conditions but do not explain the variation in prognosis.
- *CBSB holds over 8000 MPN DNA* and viable cell samples from the diagnostic archive, older research programs and clinical trials .

OBJECTIVES:

- **To characterise the mutational landscape of human MPNs**
- **To correlate with survival**
- **To generate a predictive model of prognosis by correlating disease genotype and phenotype**

METHODS:

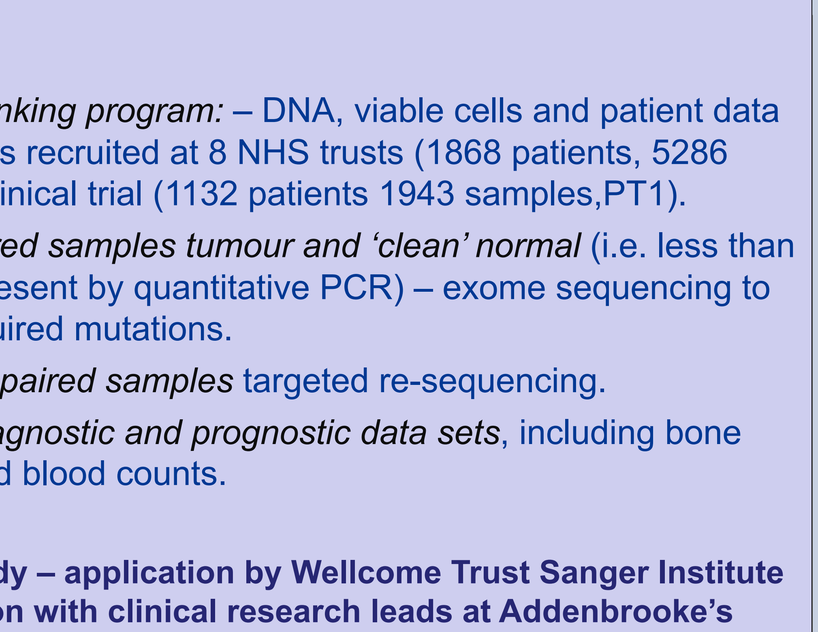
1. *10 year sample banking program:* – DNA, viable cells and patient data collected from patients recruited at 8 NHS trusts (1868 patients, 5286 samples) and large clinical trial (1132 patients 1943 samples,PT1).
2. *Phase 1 – 200 paired samples tumour and 'clean' normal* (i.e. less than 5% mutation allele present by quantitative PCR) – exome sequencing to identify common acquired mutations.
3. *Phase 2 – 1900 unpaired samples* targeted re-sequencing.
4. *Correlation with diagnostic and prognostic data sets*, including bone marrow pathology and blood counts.

Multicentre input study – application by Wellcome Trust Sanger Institute (WTSI) in collaboration with clinical research leads at Addenbrooke's Hospital and Guys and St Thomas's Hospitals NHS Trusts.

APPLICATION PROCESS:

- Application by clinical research team CUH/ WTSI and collaborators to obtain samples and study up to 2000 patients.
- MPN sample bank and Local research team approval for project
- MTA between University, Trust and WTSI drawn up.
- 3 months to approval (sample lists prepared in meantime)
- Further sample collections

CBSB application tree



ADDITIONAL R&D DATA PROVIDED BY BIOBANK TEAM:

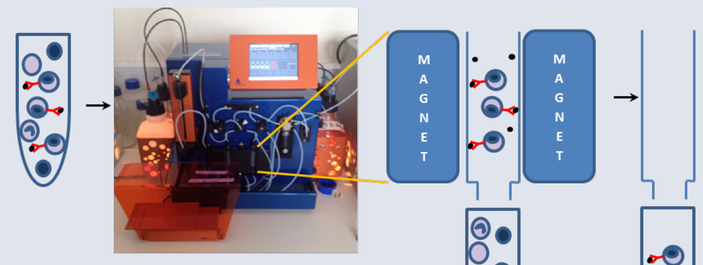
1. Search diagnostic archive for samples from consented patients.

- Extensive search of diagnostic archives to transfer samples with consent given for work. Inventory of research lab collections made and used for study.
- Consent form and clinical data search from stored paper records. Re-consenting patients on older REC studies
- Discarding materials where consent not found and after 2006.

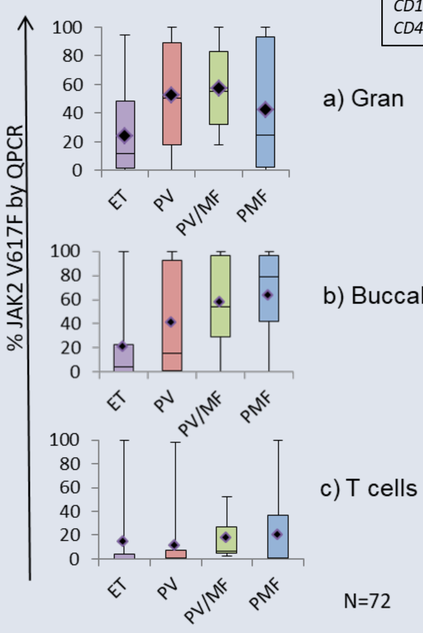
2. Sample quality assessment

- T cell isolation by AutoMACS – purity and viability assessed – below:

Fig 1:Miltenyi AutoMACS platform for T cell isolations used in the project



AutoMACS selections:
CD34 **Stem/progenitor cells**
CD2/3 **Normal T cells**
CD15 **Granulocytes**
CD45 **Leukocyte depletion of platelet suspensions**



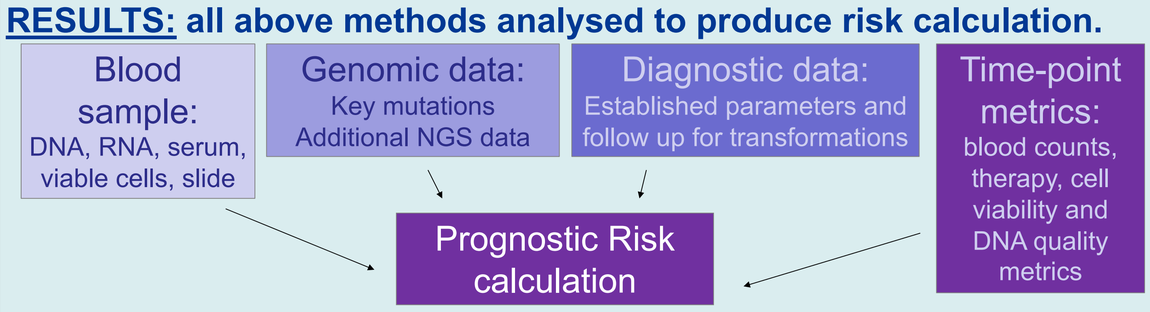
Qubit, qPCR based DNA mutation %
Best 'normal' sample – buccal or T cells
Assessed 'tumour in normal' in DNAs

3. Implemented extensive research-linked clinical database

Anonymised clinical data linked to research data:
- Mutation status
- NGS generated data
- Colony genotyping/phenotyping

Fig 2: Mutation level in different blood cell types to identify most 'normal' control by disease group

RESULTS: all above methods analysed to produce risk calculation.




ORIGINAL ARTICLE

Classification and Personalized Prognosis in Myeloproliferative Neoplasms

Jacob Grinfeld, M.B., Ch.B., Jyoti Nangalia, Ph.D., E. Joanna Baxter, Ph.D., David C. Wedge, Ph.D., Nicos Angelopoulos, Ph.D., Robert Cantrill, Ph.D., Anna L. Godfrey, Ph.D., Elli Papaemmanuil, Ph.D., Gunes Gundem, Ph.D., Cathy MacLean, M.Sc., Julia Cook, B.Sc., Laura O'Neil, B.Sc., et al.

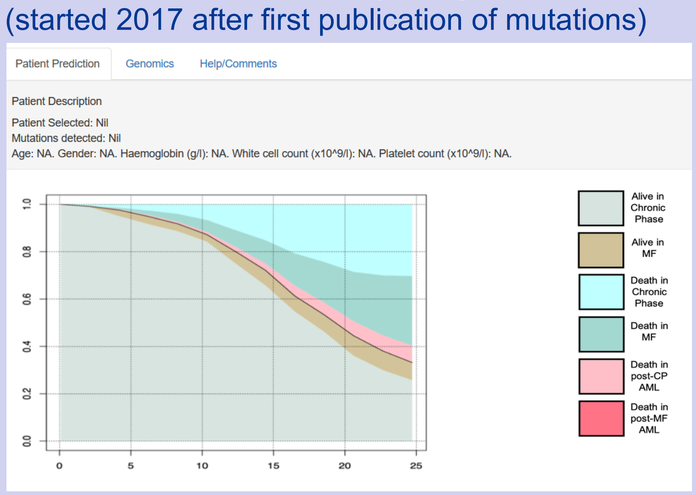
Article Figures/Media Metrics

40 References 99 Citing Articles

October 11, 2018
N Engl J Med 2018; 379:1416-1430
DOI: 10.1056/NEJMoa1716614

CONCLUSIONS: Impact of the research program –

- **Clinical diagnostic service use of biomarkers** identified by Sanger Institute team for screening myeloid diseases (started 2017 after first publication of mutations)
- **For biobank** increased applications to use unique genomic/samples set, leading to 4 papers and presentations.
- **Clinical service re-evaluation of prognostics** based on research genomic data and outcomes starting 2020; using validated **personalised risk calculator** (on WTSI website).



The biobank is sponsored by the University of Cambridge and Cambridge University Hospitals NHS Foundation Trust. Ethical approval for the study has been granted by the Cambridge East NHS Research Committee.

MANY THANKS – to past and present team members; UK Clinical Research Network;
All patients and hospital teams who have contributed to the study.

Addenbrooke's Hospital | Rosie Hospital