Approaching NETs from many angles: a medical research paradigm to challenge New Zealand's research traditions

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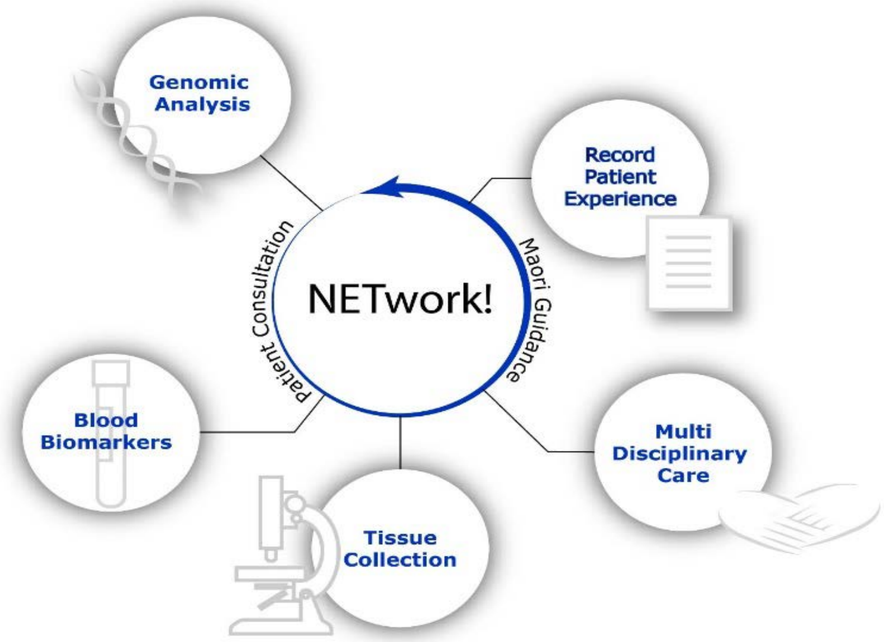
Background

The NETwork! Research Program is an initiative from a small team that established a purpose-built infrastructure to comprehensively understand NETs with the specific aim of improving patient care. In medical research environments across the world, individual research teams traditionally carry out linear programs that serially test hypotheses and programmes evolve opportunistically. It is uncommon for a small research team to approach one disease from multiple angles, starting with a blank slate, and investing in infrastructure that takes some years before a publishable output can be expected. We describe the challenges faced, mistakes made and ideas that generated success. We hope that those embarking on projects with similar complexities can learn from our experience.

NETwork! encompasses research in five complementary areas (Fig. 1):

1. Register of all patients diagnosed in NZ (2008-2012) to define the incidence of NETs in an entire population;
2. National Tumour Board (or multi-disciplinary meeting – MDM) to improve patient care, identify patients who wish to donate tissue to genomic and biomarker research, and create collaborative links between clinicians;
3. Tissue collection processes, requiring co-ordination of nursing, theatre, surgical and research teams, and the process of storing the tissue (fresh frozen and if possible, formalin-fixed);
4. Genomic tumour analyses designed to improve clinical management of NETs;
5. Patient input to introduce new project streams, ongoing promotion of the project, and increasing involvement from patients and their families.

Figure 1. Key research areas of the NETwork! Project

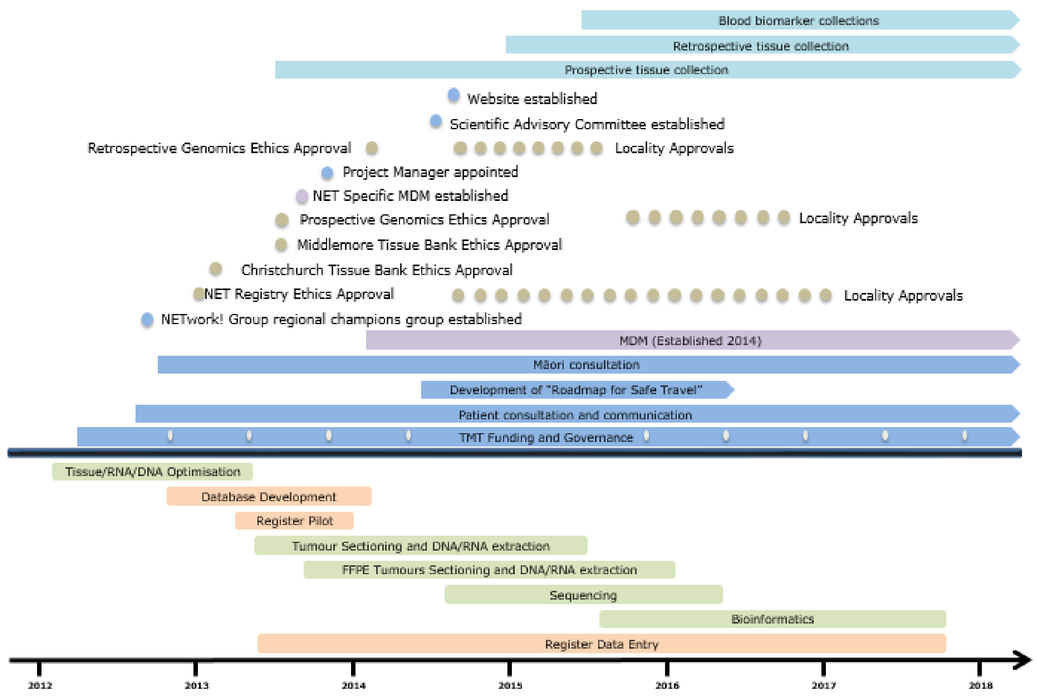


Starting with an integrated clinical and scientific vision, we established NETwork! in 2012 as a NZ wide alliance between clinicians, scientists and patients. Embedded in our work is guidance from indigenous advisors to ensure our research is moulded by the cultural needs of all stakeholders.

Figure 2. Project streams, challenges and responses

	Success Factors	Challenges	Responses
MULTI-DISCIPLINARY PROJECT TEAM	• PI's dual-trained in research / medicine • Motivated, experienced core team • Philanthropic support • Strong patient support (Unicorn Foundation) • Well-connected medical community in NZ	Different agendas and language of research vs clinical medicine	Ongoing dialogue and discussion.
		Maintaining team cohesion	Team highly motivated by dual outcomes of scientific understanding and patient wellbeing; transcending science vs medicine.
		Maintaining momentum over long timescale	Governance board and patient group feedback fosters accountability.
		Part-time core group	Maintaining effective team communication by weekly meetings and project planning.
CONSULTATION	• Highly motivated patient group via Unicorn Foundation • Positive and ongoing collaborations with Māori researchers • Relationships with cultural experts	Obtaining representation from all groups	Outreach to patient and community groups and offers of collaboration, including co-authorship.
		Pakeha core team	A close collaboration with Māori research colleagues developed the "Roadmap for Safe Travel" to identify cultural needs of Māori. Project website with Te Reo Māori translation used to keep patients up to date with research findings.
		Broad NZ cultural context – ensuring public trust regarding ethical tissue handling	Transparent consent process, with the option to discuss with Māori advisor before consenting; careful explanation of how tissue is used.
		No consensus Māori opinion – whole community input desirable	Ongoing challenge to learn how best to serve cultural needs of Māori and reciprocate value for the health needs of the Māori population.

	Success Factors	Challenges	Responses
MDM	• PI links with MDM clinicians. • Technology available to facilitate national MDM	Time-consuming, expensive (coordinators, clinician time) and requires high drive to establish new MDM	Teleconferencing links to Auckland MDM has provided MDM support for non-Auckland based clinicians. Applications for funding for MDM coordinator and local clinician time to speed up process.



	Success Factors	Challenges	Responses
REGISTER SET UP	• Single health ID for all NZ patients • NZ-wide Cancer Registry • Connections with researchers in academia and medical practice with interest in and ability to use the data to its full potential	Requirement to obtain individual locality approval from 20 DHBs	Start application process early in project as soon as ethics granted. Ongoing communication with all local PIs.
		Time-intensive to collate all data	Employed data managers across the country.
		NZCR data incomplete for NETs due to tendency to classify them as 'benign'; lead us to underestimate number of cases to enter in registry during initial planning stages.	In addition to NZCR, we performed searches of pathology databases in public and private path labs, using a pathologist-approved list of relevant search terms.

	Success Factors	Challenges	Responses
ETHICS	• Good engagement in consultation process from patients and cultural specialists	Complicated ethics of genetically testing tissue from deceased patients	Consulted with patient groups; detailed and ongoing consultation and ethics committee discussion.
		Limitations of de-identifying data – lack of follow up and inability to inform patient or family of significant findings.	Remains a limitation if you are using non-consented retrospective tissue. Ideal is to have direct patient consent.

	Success Factors	Challenges	Responses
GENOMICS	• Support / drive of patients for biomarker project • Increased availability of advanced techniques for DNA and RNA extraction from archived tissue, enabling the use of a wider cohort of patients.	Competing with well-resourced, large overseas research groups	Need to be smart in what questions we decide to answer.
		Limited access to samples (small population/ relatively low incidence).	Accessing archived tissue blocks for analysis increases cohort.
		Responsibility for raising findings to discuss rests on research team	Established independent Incidental Findings Committee for discussion of return of results. Close collaboration with clinical geneticists during analysis process, to provide outside specialist advice regarding potentially significant findings.
		Under NZ law unconsented tissue must be de-identified meaning incidental findings cannot be fed back to affected family members.	This may need wider review and consultation as genomic technologies become more widespread with unique set of problems and needs.
		Implications of incidental findings to research budget. At what point do findings from research become a public health responsibility to pursue further?	Costs for further testing on incidental findings has been covered by the research budget but this could potentially cripple research teams and needs to be examined on a national scale. The testing has stepped from research into the realm of clinical relevance for the patients involved.

	Success Factors	Challenges	Responses
TISSUE COLLECTION	• Surgical and pathology colleagues with NET specialist interest keen to be involved	Collecting fresh tissue samples alone takes a long time due to NET incidence	We diversified to collect archived tissues and found techniques that would enable gathering of genomic data from these.

Conclusions

Our approach allows different strands of research to build synergistically – e.g., the registry annotates tissue blocks for genomics, the tumour board connects clinicians to translational research projects. This can allow investigation of difficult questions that are often put in the 'too hard basket'. The research environment generated by establishing such a team is also a unique training ground to develop future translational researchers, and provides a highly enjoyable and energising work place. However, it is not easy to generate or maintain and requires relationship building and ongoing engagement between non-clinically trained scientists, patients, funders and clinicians. The delay to publishable outputs requires patience from the University and funding bodies.

Research conducted in NZ and internationally has changed, and will change further; there is a need to enhance collaboration between scientists and clinicians, between researchers nationally, with international research groups, health service providers and patients and consumers. There is also a need for communities, health providers, patients and their representatives to be engaged in health research from beginning to end through a co-design or co-development approach. Health research in New Zealand should also be conducted in partnership with indigenous researchers. We have tried to reflect these ideals in the design of NETwork!.

Establishing the NETwork! project has been an engaging, challenging and ultimately rewarding venture for the whole project team of scientists, clinicians and patients. We have taken advantage of the small well-connected medical community within New Zealand. The 'whole population' denominator of the epidemiological analysis and tissue collection puts New Zealand in a unique position compared to most countries/research groups overseas. We hope that sharing our experience developing the infrastructure the project that will in some ways be able to help others in the future.

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