The ‘molecular autopsy’: It’s uses and ethical implications.

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History

- Very short time frame in which this has occurred.
- 2 schools of thought.
  - ‘Molecular autopsy’ in all cases
  - Multi-disciplinary approach

Technology

- Exponential increase in the number of tests being performed.
- Started with panel testing of 6-7 genes for disorders such as long QT syndrome through to whole genome testing
- Decreasing cost.

Gene testing for genetic heart conditions at VCGS
Information for referring practitioners

VCGS Leaders in Genetic Health

The Molecular Genetics Laboratory at the Victorian Clinical Genetics Services (VCGS) is offering gene testing for a range of genetic heart conditions using massively parallel or "next generation" sequencing. Four cardiac gene panels are available [Additional: Congenital cardiac disease panel from September 2014]:

Arrhythmia (ARR) syndrome panel - 28 genes

AKAP9	CASQ2	KCNA5	KCNE3	KCNQ1	SCN4B
ANK2	CAV3	KCND3	KCNH2	NPPA	SCN5A
CACNA1C	GJA5	KCNE1	KCNJ2	RYR2	SNTA1
CACNA2D1	GPD1L	KCNE1L	KCNJ5	SCN1B	
CACNB2	HCN4	KCNE2	KCNJ8	SCN3B	

Cardiomyopathy (CM) panel – 65 genes

ABCC9	DES	GAA	MYH7	PLN	TMEM43
ACTC1	DMD	GLA	MYL2	PRKAG2	TMPO
ACTN2	DSC2	HCN4	MYL3	PTPN11	TNNC1
ALPK3	DSG2	ILK	MYLK2	RAF1	TNNI3
ANKRD1	DSP	JPH2	MYOM1	RBM20	TNNT2
ANO5	DTNA	JUP	MYOZ2	SCN5A	TPM1
BAG3	EMD	LAMP2	MYPN	SGCD	TTN
CALR3	EYA4	LDB3(ZASP)	NEBL	SLC25A4	TTR
CAV3	FKTN	LMNA	NEXN	TAZ	TXNRD2
CRYAB	FRYL	MYBPC3	PDLIM3	TCAP	VCL
CSRP3	FXN	MYH6	PKP2	TGFB3	

Aortopathy (AOR) panel – 11 genes

ACTA2	COL3A1	FBN2	SLC2A10	TGFB2	TGFBR2
CBS	FBN1	MHY11	SMAD3	TGFBR1	

Sudden death panel - 101 genes
All of the genes in the above panels

Congenital cardiac disease (CCD) panel – 17 genes [September 2014]

GATA4	HAND1	JAG1	NKX2-5	TBX3	TFAP2B
GATA5	HAND2	MEF2C	SALL4	TBX5	ZIC3
GATT6	IRX4	MYOCD	TBX1	TBX20	

Dilemma

- 10-20% pickup of a pathogenic mutation in selected cases.
- Should the index case be tested or family members?

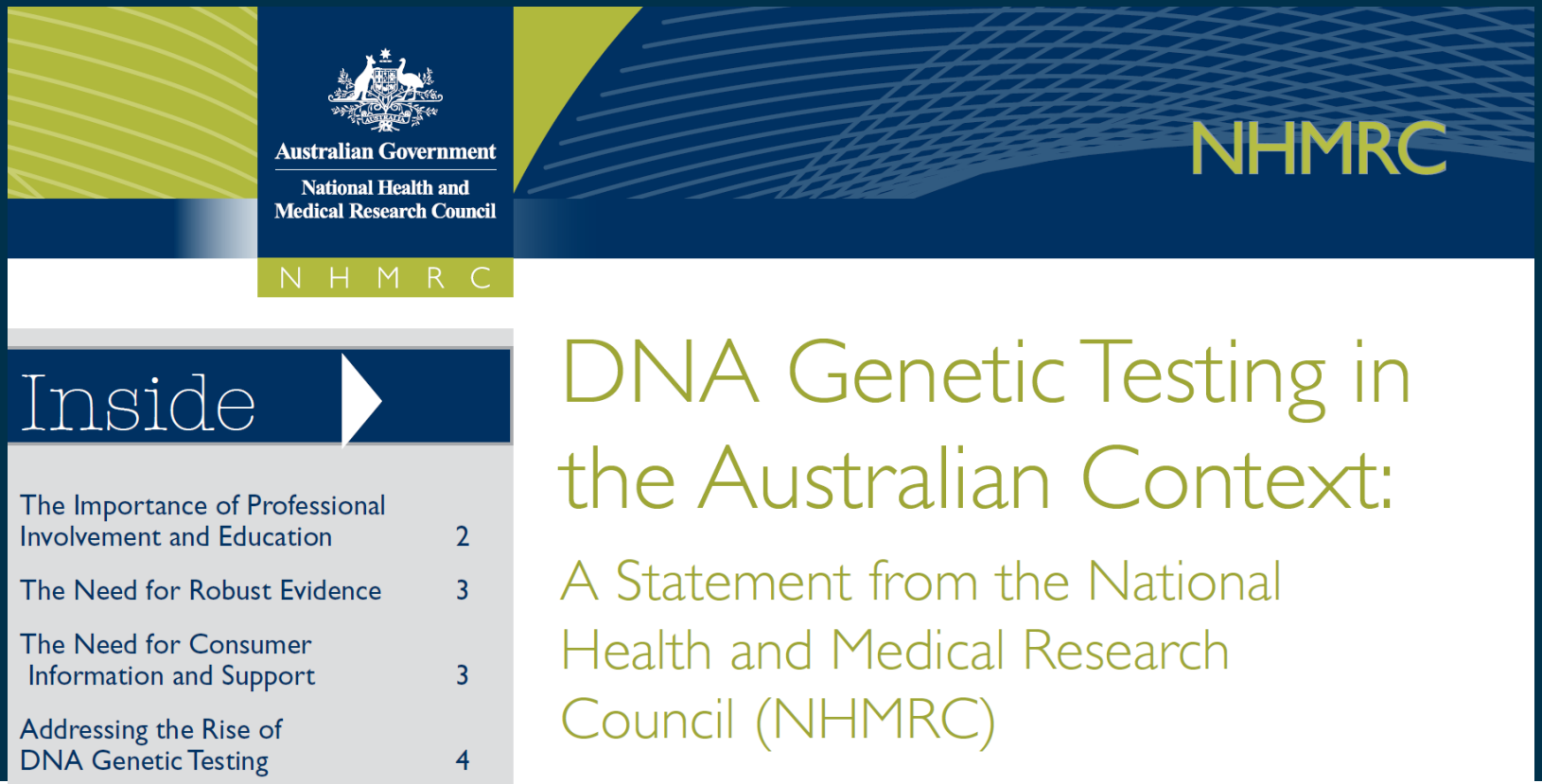
Screening Families

- Advantages
  - Helps to target molecular tests performed
  - Allows for identification of pre-symptomatic carriers of the condition.
  - Allows for proper genetic counselling

Genotype v's Phenotype

- What does a negative test result mean?
- What does a positive test result mean?

Government Guidelines



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- NHRMC considers the three following elements integral to the appropriate delivery and use of genetic testing
  - Profession involvement and education
  - A robust evidence base
  - Consumer information and support.

Ethical issues

- The identification of a genetic variant in one individual has implications of their genetic relatives.
- Who do we inform?
- What medical advice do we give and who is the most appropriate person to do this?

Privacy legislation

- Currently covers living but not deceased individuals.

- Guidelines are available also from the AMA.

VIFM approach

- Inform family members that a genetic cause of death is suspected and cardiac evaluation of living family members is required.
- Blood should be collected and stored on the deceased person (currently ETDA tube is recommended)
- Following clinical evaluation and review of family members a decision can be made about the likelihood that genetic testing is likely to give a positive results.
- The decision to perform a molecular autopsy therefore becomes a multi-disciplinary one.

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Questions.

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