HAEMOPHILIA FOUNDATION AUSTRALIA

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6 December 2019

Consultation: Review of the regulation of certain self-testing in vitro medical devices in Australia

Thank you for the opportunity to contribute to the consultation on the *Review of the regulation of certain self-testing in vitro medical devices in Australia.*

The Haemophilia Foundation Australia submission is attached.

Yours sincerely

[redacted]

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HAEMOPHILIA FOUNDATION AUSTRALIA

Submission to the Therapeutic Goods Administration

Review of the regulation of certain self-testing in vitro medical devices in Australia

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Summary of comments

Thank you for the opportunity to contribute to the consultation on the ***Review of the regulation of certain self-testing in vitro medical devices in Australia***.

This is a new area which is evolving quickly. In our view, it is very timely to commence a national discussion about self-testing, and in particular direct-to-consumer genetic testing, to explore the issues raised and consider how they might be addressed. We believe that the diagnostic, clinical, psychosocial, medico-legal and ethical issues are very complex and would recommend that they be referred to expert groups for further investigation.

We would like to comment on two types of self-tests in particular:

Self-tests for other infectious diseases

This Review has proposed the availability of self-tests for hepatitis C virus (HCV) as a way to increase testing rates and improve outcomes, particularly in hard-to-reach populations.

Self-testing for HCV could have some benefits in increasing testing rates and potentially treatment uptake for people in the community who may not be aware of their risk for hepatitis C or are not in regular contact with health services proactive around hepatitis C. This includes people with mild bleeding disorders who may have been exposed to HCV through blood products used to treat their bleeding disorder prior to 1993 but have been lost to follow-up.

- Innovative ways of reaching this community with self-tests could be explored
- This form of testing may be more acceptable to this group, especially if they perceive themselves as low risk: more convenient, private, avoiding stigma and discrimination.

However, there are also some concerns:

- How the individual would be able to interpret the results; and understand that they may need a further PCR RNA test to confirm the results
- A positive diagnosis in isolation could be very distressing.

To mitigate risks,

- self-testing would need to be embedded in an appropriate care pathway, with provision for test-related counselling
- there would need to be appropriate information in the self-test packaging
- this would involve an investment in education and support for the self-test and managing results, both for the individual and doctors in the community.

Direct to consumer genetic tests

The Review asks whether to permit Direct to Consumer Genetic Tests in Australia as a way of regulating the tests and reducing harm. Considering the appeal and increasing use of overseas-sourced self-tests in the community, it may be an inevitable response.

From the perspective of bleeding disorders, there may be some benefits:

- early diagnosis and prevention of potential bleeding episodes and resulting complications

- potential for referral to a specialist centre for best practice treatment and care
- informed family planning.

There are significant concerns:

- how to achieve informed consent prior to testing, particularly around implications of the test for the individual and their family, disclosure obligations, genetic data use
- how the individual will understand what the results mean when diagnosis is very specialised and complex
- the capacity of the health system to provide follow-up for results, particularly with gene variations that are very common in the community but may not indicate a health condition
- privacy implications of genetic data use by commercial companies.

To mitigate risks,

- packaging with the tests that includes plain language information on risks and implications of the test and its results, what to do with the test results and follow-up with their doctor, helpline contact details, and genetic data use and privacy
- a national investment in a professional helpline, education for primary care providers, and resourcing for specialist services and genetic counselling to manage the increase in referrals.

We would not support **single gene tests** being available as a self-test. Requesting this test indicates that the bleeding disorder is known or suspected. Undertaking this testing within the context of a specialist team will be important to ensure there is appropriate clinical management and follow-up.

HFA comments related to this consultation

This is a new area which is evolving quickly. We are aware of the appeal of self-testing and its increasing use in the community, and that it may be sourced over the internet and from overseas. In our view, it is very timely to commence a national discussion about self-testing, and in particular direct-to-consumer genetic testing, to explore the issues raised and consider how they might be addressed.

We have provided some comments from our perspective as a patient organisation below. However, we believe that the diagnostic, clinical, psychosocial, medico-legal and ethical issues are very complex and would recommend that they be referred to expert groups for further investigation.

We would like to comment on two types of self-tests in particular:

Self-tests for other infectious diseases

Considering the experience with HIV self-testing should self-tests for other infectious diseases be supplied and used in Australia subject to appropriate risk mitigations?

Are there any tests for particular infectious diseases that should not be available as a self-test? Please provide reasons why not.

Do you have any additional suggestions on how potential risks to consumers could be mitigated if self-tests for other infectious diseases were allowed to be supplied in Australia?

New treatments for hepatitis C are highly effective and mean that nearly everyone with hepatitis C can be cured. Australia is working towards the World Health Organization goal of eliminating hepatitis C by 2030. However, treatment uptake has been lower than expected. The current National Hepatitis C Strategy underlines the need to find everyone who is currently undiagnosed, partially diagnosed (with no HCV RNA test to confirm their viral status) and/or not actively managing their hepatitis C as essential to improving treatment uptake.[1]

The availability of self-tests for hepatitis C virus (HCV) has been proposed in this Review as a way to increase testing rates and improve outcomes, particularly in hard-to-reach populations. This could be where a person undertakes an HCV test outside the health care setting, for example at home, and performs the test themselves. They might perform a finger prick test or dried blood spot test and provide the blood sample to a laboratory, with results sent to them later; or undertake a rapid diagnostic test using saliva and interpret the results themselves.[2]

In Australia a large proportion of people with bleeding disorders who used blood products used to treat their bleeding disorder before 1993 were exposed to HCV through infected batches. Haemophilia Treatment Centres (HTCs) report that nearly all of those who are in regular contact with the HTC have now been treated and cured, or had cleared the virus naturally. However, there remains a substantial group who have been lost to follow-up, largely people with mild conditions who may have had few blood product treatments in their lifetime and be unaware of their risk for HCV. If affected, they will now have had hepatitis C for more than 25 years and will be at risk of developing advanced liver disease such as cirrhosis and liver cancer. Ascertaining the HCV status of this group and providing treatment, if appropriate, is becoming increasingly important.[3,4,5,6]

BENEFITS

Self-testing for HCV could have some benefits as a way of increasing testing rates in this group:

- Innovative ways of reaching this community with self-tests could be explored
- It could be more convenient and private for the individual
- Individuals may also perceive self-testing as a way of avoiding stigma and discrimination in comparison to requesting an HCV test at a health care service
- It may be more acceptable form of testing to them if they perceive themselves at low risk for HCV infection and are just checking their status.

CONCERNS

However, there are also some concerns with self-testing:

Interpreting the results

- If the initial self-test is an HCV Antibody test, this only indicates exposure to HCV, and would need to be followed by a PCR RNA test to determine whether the individual has ongoing HCV infection.
- HFA community consultation has reinforced that many people are unclear about the meaning of HCV Antibody Test results and may not realise that they need another test to confirm their hepatitis C status.[7,8]
- Reflexive testing, where a laboratory with a positive HCV antibody test automatically runs a PCR RNA test, may be a way to give clearer results for self-testing.
- However, reflexive testing will not be possible if the person undertakes a rapid test and interprets the result themselves.
- Saliva-based rapid testing is likely to be more acceptable than blood testing for people with bleeding disorders due to bleeding issues and ease of testing.
- Clear, plain language information about the meaning of the test results and what to do next would need to be included in the test kit. However, this is no guarantee that the individual would read and follow the information.

Potential for false negative results

The accuracy of the test would need to be very high for it to be of value and not cause harm.

For people with bleeding disorders, like others with long-term infection, the benefit of testing will be to identify chronic HCV infection and prevent the development of advanced liver disease through treatment or manage existing liver disease. With a false negative result there is a risk that they may not investigate their HCV status further. Symptoms of liver disease such as fatigue may be mistaken for the normal experience of ageing.

The current National Hepatitis C Testing Policy notes that where an individual has accessed a self-administered HCV test from overseas for their personal use, their treating doctor should confirm both a negative and positive result by standard HCV testing in a NATA accredited diagnostic laboratory.[9] Confirming test results from self-tests may need to be taken into consideration, although this may undermine the acceptability of the self-test for hard-to-reach populations.

Need for pre- and post-test counselling

The National Hepatitis C Testing Policy includes informed consent and post-test discussion as a basic principle to guide HCV testing in Australia.[9]

- The HFA hepatitis C needs assessment found that for people with bleeding disorders, being diagnosed with hepatitis C had a profound psychological impact and often triggered feelings of anger, mistrust of the health care system, and sometimes panic and despair.[7,8]
- Participants in British research into remote HCV self-testing also raised concerns about the experience of receiving a positive test result in isolation, with no direct link to care or support.[2]

An important aspect of any self-testing program will be how to manage pre- and post-test counselling and the delivery of a positive result in a way that assumes that there is a high likelihood of distress.

Care pathways

Self-testing would need to be embedded in an appropriate care pathway for it to have a beneficial effect. This would involve an investment in:

- Education about the self-test and the results, both for the individual and doctors in the community
- Appropriate information in the self-test packaging
- Provision for test-related counselling
- The capacity in the health system to follow up the test results with further testing and treatment and referral for counselling, if needed
- Engaging doctors in the community in supporting self-testing and its follow-up.

People with bleeding disorders affected by hepatitis C is a small population. If self-testing was to be promoted to the wider community, to reach for example the at-risk ‘baby boomers’ - people who injected in the 1970s and 1980s and no longer inject – and people who may have acquired hepatitis C through their medical treatment, it would need considerable preparation by both self-test manufacturers and distributors and government to ensure that there was the capacity in the health system to support it.

Direct to consumer genetic tests

Should Direct to Consumer Genetic Tests be permitted in Australia (following evaluation by the TGA) to provide consumers with an alternative to overseas testing which has not been evaluated by the TGA for its quality and performance?

Are there any particular genetic tests that should not be available as a self-test? Please provide reasons why not.

Do you have any suggestions on how potential risks to consumers could be mitigated if genetic self-tests were allowed to be supplied in Australia?

We are aware that Direct to Consumer Genetic Tests are being sold to people in the community and that they can order a range of tests online from overseas. This includes tests for genetic conditions such as bleeding disorders and whole genomic sequencing. These tests could uncover bleeding disorder gene variants previously unknown to the person undertaking the test.[10,11]

This is a new and increasingly popular phenomenon. The question of whether to permit Direct to Consumer Genetic Tests in Australia as a way of regulating the tests and reducing harm raises a complex raft of inter-related issues. We believe this is an important question to resolve, but the range of genes and their various implications will require further investigation and debate by relevant experts and other stakeholders, including patient organisations.

In inherited bleeding disorders genetic tests are not predictive. Rather they indicate that the person may have a bleeding disorder caused by the gene variant or that they may carry the gene variant without symptoms and can pass it on to their children through reproduction.

People in the community are not always aware of their risk of having inherited a bleeding disorder:

- Approximately 30% of new cases of haemophilia are spontaneous mutations and there is no family history.
- Up to 1% of the population is estimated to have von Willebrand disease (VWD), mostly undiagnosed.
- Most bleeding disorders are recessive; some only occur where both parents have the gene and they may be asymptomatic and unaware that they carry the gene.
- People with mild conditions may be undiagnosed until a serious bleeding episode occurs, such as after a serious injury, surgery or post-partum haemorrhage after childbirth.

For a person with a bleeding disorder the journey to diagnosis and referral to a specialist centre for treatment can be traumatic, involving bleeding episodes which could have been prevented if the condition had been diagnosed earlier. People with mild conditions sometimes experience years of misdiagnosis and unnecessary bleeding.

BENEFITS

In this context Direct to Consumer Genetic Tests which test for a range of gene variants related to bleeding disorders could have some benefits:

- Early diagnosis
- Prevention of potential bleeding episodes and the resulting complications, including brain and other injury to an infant during childbirth, and haemorrhage, muscle, joint

and organ damage and possibly death in people with undiagnosed bleeding disorders
- Potential for referral to a specialist Haemophilia Treatment Centre for best practice treatment and care
- Informed family planning.

CONCERNS

However, we have several significant concerns.

Informed consent

The principle of informed consent needs to be applied to these tests. In bleeding disorders issues include:

- Implications of a positive result and what to do if this occurs.

- Implications for disclosure to insurance companies and employers – individuals will be required to disclose genetic test results when applying for insurance such as life and income protection insurance, if asked, for example. Already people with bleeding disorders experience difficulties with life, income protection and travel insurance due to their bleeding disorder, and in some case, due to comorbidities with bloodborne viruses.

- Implications for other family members – they may also need to be tested; and could their genetic status be known through inheritance patterns, eg as obligate carriers, even if they decide not to have testing themselves? What are the legal and ethical obligations to inform other family members?

- How the genetic data will be used and/or shared.

Being diagnosed as carrying the gene for a bleeding disorder can have a substantial emotional impact, even if the person does not have the associated health condition. Moreover, inheritance patterns are complex and not well understood in the community without education.

It would be important to provide genetic counselling prior to testing and individual counselling if there is a positive result.

Interpretation of results

How will the individual know what the results mean for them?

A genetic test result which identifies a gene variant related to a bleeding disorder does not necessarily indicate that the person has a bleeding disorder. However, it may mean that the gene can be passed on to their children and cause a health condition, or that other members of their extended family may have the gene and need to be tested.

Bleeding disorders in people with mild conditions may not impact on them until they have a serious injury or invasive procedure. If the person taking the test self-diagnoses and assumes that their lack of serious symptoms to this point in their life means that they do not have a health condition, the value of the test in preventing bleeding episodes is lost.

There may also be false negative and false positive results.

It would be important to provide simple and clear information both before and after the test recommending that they consult a doctor about their results and giving referral pathways.

Capacity of the health system to follow up

Diagnosing bleeding disorders is complex and reliant on the expertise of a specialist medical and laboratory team. For best practice, following up the test result will need referral to a specialist team at a Haemophilia Treatment Centre. Doctors in the community will need to be educated about these genetic tests and referral pathways. The Haemophilia Treatment Centres will need the capacity to manage the increase in patients requiring further testing, which is often complex and may take many months to finalise.

Von Willebrand factor (VWF) gene variants are particularly relevant:

- The range of VWF gene variants is likely to be found in a large proportion of the Australian population
- Only a small proportion of people with VWF gene variants are likely to be symptomatic and require treatment
- Diagnosis of VWD is particularly complex; there is often a need to retest to achieve an accurate diagnosis
- VWD diagnostic measures in Australia may currently vary between Haemophilia Treatment Centres. International guidelines are in development but are not likely to be available in Australia until 2021. This will need to be taken into account when considering any national promotion of direct-to-consumer genetic testing.

Data use

Direct to consumer genetic tests are usually provided by private companies who may have an interest in harnessing the genetic data. Some transparency about their use of the data would be particularly important.

- What would the company do with the individual genetic data?
- Would it be shared or sold to third parties?
- If shared, would it be identifiable?

This has privacy and consent implications not only for the individual, but also for their family members who may share the same genetic mutations. There is also growing worldwide concern about the potential to use DNA mapping through public online databases to identify family members who have not given their consent to testing, and the implications of this for genetic disease testing need to be considered.[12]

MITIGATING POTENTIAL RISKS

If Direct to Consumer Genetic Tests were to be permitted in Australia some steps may mitigate the potential risks.

We suggest:

Packaging with the tests includes summary plain language information on:

- Risks and implications of genetic testing for the individual and their family members
- That a positive result for a gene variant may not indicate that the person has or will have a health condition
- Relevance of some genetic tests to inheritance and family planning

- That there is the risk of false positive and negative results
- A recommendation to discuss the test and its results with their doctor
- A helpline telephone number where they can discuss all of the above issues and have advice on referral pathways before and after testing
- A simple explanation about what will happen to their genetic data, along with a separate sheet explaining this in detail.

Test results should also be accompanied by this information, with a strong recommendation that they discuss the results with their doctor, whether they have a positive result or not.

There would need to be a substantial national investment in:

- A helpline employing counsellors with experience in genetic testing and who have information and training about referral pathways for the range of genetic diseases.
- Education about direct-to-consumer genetic testing and appropriate referral pathways for general practitioners, women's health/gynaecology and obstetrics services and other primary health care practitioners who are likely to be consulted for advice when people are considering a test or receive their test results
- Increased resourcing for Haemophilia Treatment Centres to manage the increase in referrals as a result of self-testing.
- Increased resourcing for genetic counselling so that it can be available prior to self-testing.

SINGLE GENE TESTS

We would not support single gene tests being available as a self-test. Requesting this test indicates that the bleeding disorder is known or suspected. Undertaking this testing within the context of a specialist team will be important to ensure there is:

- accurate interpretation of the results
- appropriate clinical management before and after the test, including counselling and support if needed
- information about variants that may result in inhibitors or antibodies to treatment is identified, passed on to the individual and recorded in the Australian Bleeding Disorders Registry for clinical management in the future
- and that data can be collected to improve the clinical knowledge base and improve treatment and care in the future.

Further references for our comments Direct to Consumer Genetic Tesing are available in the attached BACKGROUND document.

CONCLUSION

Thank you for the opportunity to comment and we hope that you will consider these important issues in your review of the regulation of certain self-testing in IVDs in Australia.

Background

HAEMOPHILIA FOUNDATION AUSTRALIA

Haemophilia Foundation Australia (HFA) is a not-for-profit organisation which represents people with haemophilia, von Willebrand disease and other rare bleeding disorders in Australia. It is the national peak organization for bleeding disorders and its purpose is to improve health outcomes and the quality of life for people living with bleeding disorders through representation, education and the promotion of research.

INTRODUCTION

Relevance of hepatitis C self-testing

Many people with bleeding disorders in Australia were exposed to hepatitis C virus (HCV) through infected blood products used to treat their bleeding disorder before 1993, by which time viral inactivation manufacturing processes and screening of the blood supply had been introduced.

Although Haemophilia Treatment Centres report that most affected patients known to them have now been treated for their hepatitis C and cured, there remains a substantial group of people who have been lost to follow-up and whose HCV status is unknown. These are largely people with mild conditions who may have had few bleeding disorder treatments in their lifetime and may not be aware of their risk for HCV infection. If they have hepatitis C, they will have been living with chronic infection for more than 25 years and will be at risk of developing advanced liver disease such as cirrhosis and liver cancer.

With highly effective hepatitis C treatments now available, it is becoming increasingly important to reach this group and assess their HCV status, with a view to treatment if appropriate.

HCV self-tests may provide an innovative way to reach this population, establish their HCV status and encourage uptake of treatment.

Relevance of genetic testing

Genetic inherited bleeding disorders are rare, but some are not as rare as commonly thought. The bleeding episodes caused by the disorder can be serious: life- and limb-threatening if not treated appropriately.

Where there is a known family history, a bleeding disorder can be diagnosed in utero or soon after birth and steps taken to prevent bleeding. However, in many cases parents have not realised that they or their child have the gene variant causing a bleeding disorder until a serious bleeding episode occurs, which can be very dangerous and traumatic. For females and people with mild disorders, diagnosis may not occur until adolescence or adulthood and sometimes can involve a long period of misdiagnosis during which unnecessary bleeding episodes occur.

If genetic testing were more widely available, it might assist with earlier diagnosis. However, it raises many other issues, including how the person having the genetic test would receive appropriate information, management and support relating to:

- the interpretation of the test results, as the results may or may not indicate that the person has a bleeding disorder
- referral to specialist health care services for best practice clinical management

- counselling, education and other support to manage the psychosocial impact of receiving the results
- the other implications of the test results – for relationships and having children, for other family members, for disclosure with insurance and employers.

PEOPLE WITH BLEEDING DISORDERS IN AUSTRALIA

Population

There are more than 6,000 people who have been diagnosed with inherited bleeding disorders in Australia, including haemophilia, von Willebrand disease (VWD), rare clotting factor deficiencies and rare platelet function disorders. As a result of their bleeding disorder, the blood clotting process does not work properly.[13,14]

- **Haemophilia** A occurs in 1 in 4,000 male births internationally and haemophilia B in 1 in 20,000 male births.[15]
- The prevalence of haemophilia or carrying the gene in females is not yet known.
- Approximately one-third of new cases are caused by spontaneous gene mutations occurring during reproduction, and there is no previous family history. [13]

- **VWD** is the most common bleeding disorder, but it is thought that only a small number have been diagnosed. Estimates of prevalence vary from 0.1% to 1% of the general population, depending on the criteria used for diagnosis and patient selection. Many people have very mild symptoms, and some are not symptomatic.[13,16]

- **Rare clotting factor deficiencies** are very rare. Incidence internationally ranges from 1 in 100,000 for factor XI deficiency to 1 in 3 million for factor XIII deficiency.[13]

Bleeding problems

Without treatment people with bleeding disorders can bleed for longer than normal, and some bleeding episodes can be life- or limb-threatening. In haemophilia the bleeding is usually internal, into joints, muscles and organs. In VWD bleeding usually involves the mucous membranes, the delicate tissues that line body passages such as the nose, mouth, uterus, vagina, stomach and intestines. People with severe forms of VWD may also have bleeding into joints and muscles, similar to haemophilia.

If a preventive treatment plan has not been put in place, people with bleeding disorders may also experience prolonged bleeding as a result of injury or invasive medical or dental procedures. Females with bleeding disorders may have heavy menstrual bleeding, with anaemia as a result, and there is a significant risk of increased bleeding after childbirth, including post-partum haemorrhage.[13]

Childbirth is also a time of high bleeding risk to the child, with the potential for serious brain and other injuries. When the child is known or suspected of having a bleeding disorder, the recommendation is to ensure that delivery is not traumatic to the child, for example, avoiding forceps or vacuum extraction during vaginal delivery.[14]

Severity

Individuals with bleeding disorders are clinically diagnosed as having a mild, moderate, or severe form of the disorder.

- Haemophilia is classified according to severity based on factor activity levels.[13]

- The definition of severity for VWD and other clotting factor deficiencies has not yet been standardized: international diagnostic and clinical management guidelines for VWD are currently in development and expected to be released in 2020, with Australian guidelines to follow in 2021. VWD is primarily classified by type (types 1,2 or 3) and variants within type 2, and then by severity within the type. In Australia the diagnosis of VWD sub-types and assignment of a severity rating to an individual's disorder can vary between health care services.[13,16]

Nearly all people with bleeding disorders will have this level of severity from birth.

- The mild forms occur more commonly in the population but may be undiagnosed until a serious bleeding episode occurs. This is often related to a serious injury, surgery or post-partum haemorrhage after childbirth.
- Without preventive treatment, people with moderate or severe forms of the disorder will have bleeding episodes often, and those with severe bleeding disorders may have bleeding for no obvious reason.
- Any bleeding episode can be serious, no matter what the severity of the bleeding disorder.[13]

DIAGNOSIS

Inherited bleeding disorders are caused by clotting factor gene mutations or variants, passed on from parent to child or occurring spontaneously during conception.

However, a person with the gene variant is not always symptomatic or may not have the related health condition. Diagnosis can be complex and includes several different procedures:

- Taking an individual's personal history of unusual bleeding problems
- Checking the family history for bleeding problems
- Specialized laboratory tests for the relevant bleeding disorder.

Best practice involves referral to a Haemophilia Treatment Centre, where there is a haematologist and laboratory service with expertise in bleeding disorders who can identify specific bleeding disorders and interpret the test results accurately.[13,14]

Haemophilia diagnosis
Diagnosis can involve genetic testing, particularly in haemophilia.

Genetic testing in haemophilia can serve a number of purposes:

- Providing a molecular confirmation of a diagnosis where bleeding problems have been identified
- Identifying the specific mutation or variant responsible for haemophilia in a particular family
- Determining whether the individual tested has this gene mutation
- Identifying if the individual has a variant associated with specific bleeding patterns or a higher risk of developing inhibitors (antibodies) to treatment.[14,17]

Collecting genetic test results also enables Haemophilia Treatment Centres to contribute data on these mutations to international haemophilia mutation databases to help understand the relationship of a particular mutation to bleeding patterns and inhibitor development.[18]

However, a definitive diagnosis of haemophilia relies on clotting factor level testing that demonstrates factor VIII or IX levels less than 40% of normal.

- Males with a factor VIII or factor IX gene mutation will have haemophilia. Their factor level will be consistent with other family members who have inherited the same variant
- Females with a factor VIII or factor IX gene mutation may carry the gene and be asymptomatic, or they may have low factor levels and some may have haemophilia, usually mild. Factor levels in females are not consistent with other family members and are thought to relate to random X-chromosome inactivation during their development as an embryo[14,19]

VWD diagnosis

Diagnosing VWD is particularly complex and involves several laboratory tests. Some tests may need to be repeated as they are affected by several factors, including blood type, hormones, stress, exercise and inflammation.[16] At present in Australia genetic testing in VWD is usually only used for diagnostic clarity in specific circumstances, due to error rates and the difficulty of assigning particular mutations to VWD Types.[20] However, with the improvements to testing with next generation gene sequencing, Australian clinicians are likely to include genetic testing in VWD diagnostic practice in the next few years.[21]

DIAGNOSIS JOURNEY

Where there is a known family history of bleeding disorders, diagnosis usually takes place within the context of a specialist multidisciplinary treating team at a Haemophilia Treatment Centre.

For a person without a known family history of bleeding disorders, the journey to diagnosis and referral to a specialist centre for treatment can be traumatic, involving bleeding episodes which could have been prevented if the condition had been diagnosed earlier. People with mild conditions sometimes experience years of misdiagnosis and unnecessary bleeding.

HFA's consultation has found that women particularly have experienced delayed diagnosis with a bleeding disorder, even where there is a known family history. They have usually been treated in the community, for example, by a general practitioner rather than a Haemophilia Treatment Centre. However, most doctors have not received training about managing bleeding disorders. As a result many women have had problems with diagnosis and referral, and had bleeding problems with surgery, medical and dental procedures, with menstruation and after childbirth. Many women also spoke about their difficulties in being 'taken seriously' by health professionals, as some of their non-haemophilia health professionals (eg, general practitioners, surgeons, dentists) didn't know that women can have bleeding disorders. This is similar to the experience of women with bleeding disorders in other developed countries such as Canada.[22,23]

The impact of diagnosis with carrying the gene for a bleeding disorder can be considerable, even if a person already suspects they carry the gene. Some women may not be diagnosed as carrying the gene until their child is diagnosed with haemophilia. Being fully informed and supported at this point is crucial.[24]

> *'When I was first diagnosed, I felt gutted, but I had a feeling that I was a carrier already, because of some bleeding symptoms I had experienced. Everything fell into place with a sickening thud.'*
>
> *'I found out that I carried the gene when I was 12 weeks pregnant. The stress was enormous as I had to make some important decisions fast.'*

'At that time I felt confused, shocked, bewildered and afraid. I had not known I was a carrier. There was no family history. I knew nothing about haemophilia. I didn't know what to expect or how to look after my baby [with haemophilia].'

'At the beginning I felt guilty [about diagnosis as a carrier] when family members became upset when hearing of my son's diagnosis. I also wondered what my son's future would be like.'

'When I was diagnosed at 9 years of age, I felt frightened and wished it had been someone else. I was angry that I did not have a choice in being a carrier.'

'I felt bereaved all over again when I realised that this was why my father, an undiagnosed haemophiliac, inexplicably bled to death after surgery at the age of 54.'

'It was a big shock even though my brother has haemophilia. It took me weeks to come to terms with it.'

'The doctor gave me my results and I just put them away. I couldn't think about it without panicking. But after a couple of weeks I decided to talk to the Haemophilia Counsellor and it was like a weight lifted off.'

Quotes from Australian women who carry the gene for haemophilia[25]

INHERITANCE

Haemophilia

- Haemophilia is a sex-linked recessive disorder. The factor VIII or factor IX gene variant responsible for hemophilia is carried on the X chromosome.
- Males with the gene will have haemophilia and will pass the gene on to all their daughters.
- Females may carry the gene without symptoms, but some may have low factor levels and have a bleeding tendency. Some have haemophilia, usually mild. Females can pass the gene on to daughters and sons.

VWD

- Most types of VWD are autosomal dominant disorders. Both males and females can carry the gene variant, with or without symptoms, and can pass it on to their children
- Type 2N and 3 VWD are autosomal recessive disorders where both parents have the gene variant and have passed it on to their child. Both males and females can carry the variant, with or without symptoms, and can pass the variant on to their children. If both parents have the variant, there is a 1 in 4 chance that their children could inherit a copy of the gene variant from both of them and have moderate to severe symptoms.

Rare clotting factor deficiencies

- Most are autosomal recessive disorders, with similar inheritance patterns to VWD
- The exceptions are factor I deficiency and factor XI deficiency, which may be either autosomal recessive or dominant.[13,17,26]

Inheritance patterns are not easily understood by affected community members and HFA has produced simple inheritance diagrams for haemophilia and VWD in collaboration with HTCs for use as patient education tools and to support genetic testing.[27]

GENETIC COUNSELLING

Genetic counselling is an integral part of comprehensive care for bleeding disorders. Genetic counselling is usually conducted before undertaking genetic testing to weigh up the pros and cons of genetic testing with advice and support from specialists, counsellors and other experts - for example:

- the role of genetic testing in understanding the person's bleeding disorder
- its effect on their perception of themselves and on their relationships
- their personal understanding of what it's like to have a bleeding disorder
- the impact on children and other family members
- their personal religious and cultural beliefs
- future disclosure obligations and implications for life or income protection insurance
- any costs involved
- and other issues relevant to their personal situation.[17,28]

The appropriate age to undertake genetic testing for haemophilia in a female is the subject of some debate nationally. A common time is when she reaches childbearing age and can understand the process and implications fully and make the decision to undertake the test herself. In some cases, the health benefit to the child of helping to predict and manage symptoms leads to earlier genetic testing.[29]

FAMILY PLANNING

Genetic counselling, prenatal diagnostic testing and IVF with pre-implantation genetic diagnosis may be involved in family planning where one or both partners have the gene for a bleeding disorder.

It is recommended that women who are known to carry the gene for haemophilia, VWD or other bleeding disorders ask their haemophilia and obstetric teams to consult with each other for a safe pregnancy and delivery of a child with a bleeding disorder.[14,28]

DISCLOSURE – INSURANCE AND EMPLOYERS

People with bleeding disorders are often required to disclose their health condition when applying for insurance such as life, income protection and travel insurance, some forms of superannuation and with some employers, such as the Australian Defence Force or the police force. They are often required to pay higher premiums and can be refused insurance or refused entry to the ADF or police force.

They are also required to disclose results of genetic testing when applying for some kinds of insurance, and this may be required for some employers where it may be relevant to a health condition.[30] HFA is monitoring this to understand in particular the implications for women who carry the gene but do not have haemophilia.

TREATMENT

A treatment plan for an inherited bleeding disorder is specific to the individual. It takes into account their medical needs, what works best for them and their personal situation.

Treatment often requires medicines that replace, stimulate the generation of or mimic the function of the clotting factor or platelet that is missing or not working properly. This includes factor replacement therapy derived from human plasma and/or genetically engineered recombinant clotting factors and related treatments. This treatment can be had as

prophylaxis, infused up to several times a week to assist in preventing bleeding episodes, or on-demand to treat the bleeding episode as it occurs. It may be personalised with pharmacokinetic analysis and with genetic testing to check whether the individual has a gene variant that has a higher risk of developing inhibitors or antibodies to specific treatment products, which would make treatment less effective.

For some people, particularly those with mild conditions or VWD, treatment may be with synthetic hormones such as desmopressin, which releases the body's stored factor VIII into the blood stream to help blood clot.

Treatment also involves exercise guided by a musculoskeletal physiotherapist with expertise in haemophilia to prevent bleeding and protect joints, and to rehabilitate a joint or muscle back to full function after a bleeding episode.[13,14,21]

COMPREHENSIVE CARE

The Australian Haemophilia Centre Directors' Organisation (AHCDO) and the National Blood Authority (NBA) have published best practice treatment guidelines for bleeding disorders, which include an explanation of the comprehensive care model for bleeding disorders. These guidelines are evidence-based and aligned with international standards of care.[14]

Current health care services for people with bleeding disorders in Australia, provided through state and territory Haemophilia Treatment Centres, are based on this comprehensive care model. The nation-wide adoption of this model reflects both the improved quality of life and the cost benefits gained through clinically appropriate care and centralised and high quality data management, including the intensive management of limited supplies of expensive clotting factor.

In 1998 the Australian Health Ministers' Advisory Council (AHMAC) recommended appropriate funding for designated Haemophilia Treatment Centres to improve the coordination of care and treatment and provide expert advice to enhance quality of care to people with haemophilia. This includes a specialist multidisciplinary team of:

- Haematologists
- Nurses
- Social workers/counsellors/psychologists
- Physiotherapists
- Involvement of other specialities, such as orthopaedics, pain management, gynaecology and obstetrics and genetic counselling, as required
- Specialised laboratory services.

There are specialist Haemophilia Treatment Centres (HTCs) located in public hospitals in capital cities in every state and territory in Australia, as well as HTCs in Newcastle, NSW and one additional Centre in Western Australia which is located in a private hospital. Best practice is that the care for the person with a bleeding disorder where bleeding risks are involved is co-ordinated through a Haemophilia Treatment Centre. This may involve liaison with their general practitioner or other non-haemophilia medical specialists as required.[13,14]

People with bleeding disorders will require care through an HTC for the duration of their life. This also ensures that they have access to new developments in best practice clinical management over their lifetime.

HEPATITIS C

A large proportion of Australians with bleeding disorders were exposed to blood-borne viruses before 1993 through blood products for their treatment, usually human plasma-derived clotting factor concentrates. This included:

- HIV in the mid-1980s
- HCV, which was most likely prevalent in the community from the 1970s but diagnosis was only confirmed when testing began in the early 1990s.[3]

A study in one Australian Haemophilia Treatment Centre suggests that:

- up to 50% of people exposed to clotting factor during this time may be HCV positive
- > 50% of those with mild haemophilia with product exposure may be HCV positive
- > 80% of those with severe haemophilia may be HCV positive due to increased product exposure.[4]

For this community, HCV diagnosis took place in the context of the HIV epidemic, which resulted in high mortality in the haemophilia population. Those with HIV commonly experienced discrimination at school, in the workplace, in health care settings and even among their friends and family and many did not disclose their HIV status, even to other family members. As a result the risk of hepatitis C was rarely discussed in the community until the Senate Inquiry in 2003.[7,8]

A substantial number of males and females with mild bleeding disorders, such as haemophilia and von Willebrand disease (VWD), have had very few treatments with clotting factor concentrates in their lifetime and may not realise they were at risk of HCV infection. They may never have had HCV testing and may not be aware of their HCV status. They are often not well-connected to HTCs and many have been lost to follow-up. [4]

These epidemics have had a profound physical and psychological impact on the bleeding disorders community.

Effects on individuals are variable and can include:

- Increased complexity of co-morbidities, which intensifies as people age, leading to mobility problems and overload with health conditions and services
- For some, unresolved anger at the route of infection and mistrust of the medical system
- Concerns about privacy and reluctance to disclose either their bleeding disorder or their bloodborne virus due to past experiences of stigma and discrimination.[7,8]

If an adult with a bleeding disorder has a current infection with HCV, infection is likely to be of at least 25 years' duration - a significant risk factor for chronic liver disease or cirrhosis.[6]

HTCs report a high treatment uptake and cure rate among their patients with hepatitis C who are in regular contact with the HTC. However, they remain concerned about the people who have had blood product treatment before 1993 and are at risk of HCV infection, but have

been lost to follow-up, particularly those with mild disorders who may be unaware of their risk factors. It is becoming increasingly important to identify and reach this group, to check their HCV status and manage any liver health disease, and to take this opportunity to eliminate hepatitis C in this population.[4,5,31]

REFERENCES

1. Australia. Department of Health. Fifth National Hepatitis C Strategy 2018-2022. Canberra: The Department, 2018.
2. Guise A, Witzel TC, Mandal S, et al. A qualitative assessment of the acceptability of hepatitis C remote self-testing and self-sampling amongst people who use drugs in London, UK. BMC Infectious Diseases 2018;18:281. https://doi.org/10.1186/s12879-018-3185-7.
3. Australia. Senate Community Affairs References Committee. Hepatitis C and the blood supply in Australia. Canberra: The Committee Secretariat, 2004. <http://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/Completed_inquiries/2002-04/hepc/report/index>
4. Northcott, MJ, Ong, WL, Walsh, M, et al. Prevalence of transfusion-acquired hepatitis C in an Australian bleeding disorders population. Haemophilia 2013;19(6):847-52.
5. Parikh S, Tran H, McRae S. Uptake of subsidised hepatitis C direct acting antiviral treatment among patients with bleeding disorders in Australia [abstract]. Haemophilia 2018;24(Suppl. 5):1-218. https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.13478
6. Poynard, T et al. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. J of Hepatology 2001; 34:730-9.
7. Haemophilia Foundation Australia. “A double whammy”: living with a bleeding disorder and hepatitis C. Melbourne: HFA, 2007. <https://www.haemophilia.org.au/HFA/media/Documents/Hepatitis%20C/A-double-whammy-living-with-a-bleeding-disorder-and-hepatitis-C-HFA-Oct-2007.pdf>
8. Haemophilia Foundation Australia. Getting it right: hepatitis C needs assessment evaluation and implementation report. HFA: Melbourne, 2009. https://www.haemophilia.org.au/HFA/media/Documents/Hepatitis%20C/Getting-it-right-Hepatitis-C-needs-assessment-evaluation-and-implementation-report-HFA-Jan-2009.pdf
9. National HCV Testing Policy Expert Reference Committee. National hepatitis C testing policy v1.2. Canberra: Australian Government Department of Health, 2016.
10. Horton R, Crawford G, Freeman L, et al. Direct-to-consumer genetic testing. BMJ 2019:367:l5688. https://doi.org/10.1136/bmj.l5688
11. Which direct-to-consumer genetic test to choose? The Medical Futurist. 20 March 2018. https://medicalfuturist.com/which-direct-to-consumer-genetic-test-to-choose/
12. Segert, J. Understanding ownership and privacy of genetic data. Science In the News. Harvard University. The Graduate School of Arts and Sciences. 28 November 2018. http://sitn.hms.harvard.edu/flash/2018/understanding-ownership-privacy-genetic-data/
13. Australian Bleeding Disorders Registry. Annual Report 2017-18. Canberra: National Blood Authority, 2018. https://www.blood.gov.au/system/files/ABDR-Annual-Report-2017-18-Final.pdf
14. Australian Haemophilia Centre Directors’ Organisation. Guidelines for the management of haemophilia in Australia. Canberra: National Blood Authority, 2016. https://www.blood.gov.au/haemophilia-guidelines
15. Iorio A, Stonebraker JS, Chambost H, et al. Establishing the prevalence and prevalence at birth of hemophilia in males: a meta-analytic approach using national registries. Annals of Internal Medicine 2019;171(8):540-546. DOI: 10.7326/M19-1208
16. Stufano F, Baronciani L, Peyvandi F. Diagnosis of von Willebrand disease: phenotypic characterization. Treatment of Hemophilia: no. 55. Montreal: World Federation of Hemophilia, 2017. http://www1.wfh.org/publications/files/pdf-1691.pdf
17. Alabek M, Mohan R, Raia MH. Genetic counselling for hemophilia. Rev. edn. Treatment of Hemophilia; no. 25. Montreal: World Federation of Hemophilia, 2015.
18. Campbell S, Parikh S, Tran H. Genetic landscape of haemophilia A and B in Australia. [abstract PB0696] Research and Practice in Thrombosis and Haemostasis. 2019;3(Suppl. 1):327.
19. McLintock, C. Women with bleeding disorders: Clinical and psychological issues. Haemophilia 2018;24(Suppl. 6):22–28. https://doi.org/10.1111/hae.13501.

20. Favaloro EJ. Genetic testing for von Willebrand disease: the case against. Journal of Thrombosis and Haemostasis 2010;8:6–12. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1538-7836.2009.03482.x
21. Favaloro EJ, Pasalic L, Curnow J. Diagnosis and management of von Willebrand disease in Australia. Annals of Blood 2018;3:31. http://aob.amegroups.com/article/view/4450/5193
22. Haemophilia Foundation Australia. Women and bleeding disorders project report. Unpublished report, Melbourne, 2002.
23. Renault, NK, Howell, RE, Robinson, S, et al. Qualitative assessment of the emotional and behavioural responses of haemophilia A carriers to negative experiences in their medical care. Haemophilia 2011;17:237-245.
24. Myrin-Westesson L, Baghaei F, Friberg F. The experience of being a carrier of haemophilia and the mother of a haemophilic child. Haemophilia 2013:19 (2):219-224.
25. Quotes from Australian women who carry the gene for haemophilia collected by Haemophilia Foundation Australia in consultation for the publication: Haemophilia Foundation Australia. Finding out you carry the gene. Melbourne: HFA, 2017.
https://www.haemophilia.org.au/HFA/media/Documents/WWBD/Finding-out-you-carry-the-gene-web.pdf
26. Goodeve AC, James P. Von Willebrand disease. GeneReviews Oct 5 2017, viewed 1 August 2018. https://www.ncbi.nlm.nih.gov/books/NBK7014/
27. See for example, Haemophilia Foundation Australia. Female factors. Melbourne: HFA, 2018. https://www.haemophilia.org.au/publications/women-with-bleeding-disorders/young-women
28. Haemophilia Foundation Australia. Haemophilia. Melbourne: HFA, 2013.
29. McCosker, J. What do we know about carriers? National Haemophilia 2019;206:21-23. https://www.haemophilia.org.au/publications/national-haemophilia/2019/no-206-june-2019/what-do-we-know-about-carriers
30. Haemophilia Foundation Australia. The law and disclosure. Melbourne: HFA, 2018. https://www.haemophilia.org.au/about-bleeding-disorders/disclosure.
31. Parikh S. Uptake of hepatitis C direct acting antiviral (DAA) treatment. National Haemophilia 2018;204:10-11. https://www.haemophilia.org.au/publications/national-haemophilia/2018/no-204-december-2018/uptake-of-hep-c-treatment.