A Submission to the Australian Human Rights Commission via the Australian Children's Commissioner: Regarding - The examination of intentional self-harm and suicidal behaviour in children.

Authors:

Thursday, June 05, 2014

Keywords: genotype, metabolism, antidepressant, sertraline, desvenlafaxine, suicide, self-harm, depression, akathisia, pharmacogenomics, autism.

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INTRODUCTION

Teen suicide and self-harm are major issues. They are a high social and economic burden on individuals, families and the wider community. The aetiologies of teen suicides, self-harm and depression are widely varied and multi-factorial.

This submission raises several issues relevant to the issues of self-harm and suicidal behaviour in adolescents. It includes the personal story and perspective of the first author, with a medical clinician's perspective from the second author.

On request, the authors are happy to provide further references and supporting evidence for the issues raised and facts presented.

A PARENT'S VIEW

The Story to Date:

In my daughter, (15 years old), told me that she needed to go to the doctor to talk about how she was feeling. On advice from a friend, who is a clinical psychologist in Sydney, we went to our general practitioner (GP) to get a Mental Health Care Plan and referral to a psychologist. firmly told me that she wanted to talk to the doctor by herself. After a while, I was called in to the room and told that was severely depressed and was handed a Mental Health Care Plan, referral to a psychologist and a prescription for 50mg tablets of sertraline.

On reading about this medication I learned that 'suicidal ideation' was a possible side effect of this medication. The second night that she took sertraline did not sleep at all. I rang the pharmacist to check if this was usual and, on his suggestion, I halved the dose to 25mg. I also made an appointment with another doctor at the same medical practise and the doctor agreed with halving the dose and advised regular monitoring through weekly appointments as the first doctor had gone on leave.

On the third night of taking sertraline, came downstairs obviously distressed and wringing her hands. She was exhibiting the 'physical' signs of akathisia. I took her down to the Hospital at about After her initial triage, spent about four hours pacing and wringing her hands. This experience has left an indelible mark on her as she half-jokingly referred to herself as the 'luny woman' everyone was avoiding. Finally, was taken to one of the three psych beds in emergency. There was concern that she was suffering from serotonin toxicity. She was given three doses of diazepam in rapid succession to calm her and stop the akathisia movements. had also experienced visual hallucinations which frightened her. The care we received was alright but looking back it was obvious the medical staff had no idea what they were doing and was being boxed as an emotionally overwrought teen who was seeking attention. During this emergency attendance we were visited by a young doctor She told us that she was interested in pharmacogenomics, that is, how medication handling can be affected by an individual person's genetics. asked if she could take saliva for genetic testing and said that she forward the results to me. I agreed to this as an interesting scientific aside.

An experienced psych nurse spoke to and told me that, in her experience, was not experiencing serotonin toxicity. It was during this interview with that I first heard the words 'have you thought of suicide and do you have a plan'. I was horrified. Suicide had not been part of the discussions with until that moment. Later, I was told that it is a procedural question that brings the question of suicide out into the open and allows the practitioner to assess the risk of suicide and self-harm. father believes this phrase does more harm than good by placing the idea in teen minds. The nurse suggested that we could contact Headspace.

It would have been another couple of hours until was seen by a paediatrician. was admitted to the paediatrics ward for one hour and then discharged. She was told to stop taking the sertraline. My husband recalls the paediatrician saying that 'she would not have prescribed that and have used fluoxetine instead'. In other words if one drug does not work throw another one at the problem.

The following weekend we were back at the Emergency Department. Throughout the week had suffered more episodes of akathisia, hallucinations and came down with a cold which turned into pneumonia. barely moved from her bed. On the Saturday night I got a text message from (texting has been a great way for to let me know when she is in trouble mentally) telling me to come up stairs. It turned out that she had taken a bed sheet and tied it to her wardrobe handles to see if they would hold her weight so she could hang herself. I got her to ring Lifeline while I rang the emergency mental health people. The end result was that I took her back to the Hospital. Again we waited for 2-3 hours before being taken into a 'psych bed'. The same questions were asked, and again when we saw another paediatrician some three hours later. She explained to us that there was little they could do for and that we should take her home and keep a close eye on her. That night I slept on her bedroom floor.

During this time I had managed to get an appointment with a psychologist. The waiting lists were long and it was difficult to work out who might treat teens. There is a shortage of psychologists/psychiatrists that treat teens. At no time did the staff offer any referrals or information regarding outpatient assistance for suicidal teens. As a parent I felt completely helpless. My psychologist friend, in Sydney, put me onto

On the Monday, was in trouble again with her thoughts and we went back to the and left after a couple of hours with no help offered. I rang and got an appointment for a couple of days later. After ringing the psychologist that we were waiting to see, we got an earlier appointment.

At we saw a psychiatrist who recommended cognitive behavioural therapy. took an instant dislike to her. Looking back I can understand why. The psychiatrist left me with the impression that she saw an intelligent girl who had been busy self-diagnosing on the internet and that the restlessness was a put on. I think understood this and shared this impression. I have found this dismissive attitude quite disturbing. As a mother I had a sense that because came from a stable, supportive home in a particular postcode, she was excluded from their care. We have not been back to but I did find one individual who was part of their triage team, very helpful and supportive.

During this period did not attend school and her year co-ordinator, was supportive. Unfortunately for the staff, the school experienced two student suicides within a month of 'meltdown'. A friend and I attended a meeting regarding

these deaths at the school. This was run by Headspace who was supporting the staff and students. My friend, whose sons are good friends of was and is concerned about the mental health of one of her boys. She pointed out that the school and Headspace seemed unaware or unconcerned about as I had not been contacted in regards to support offered in regards to the two suicides. As herself pointed out, both teens had been within a group of friends that had mental health and family problems.

I did make contact with the school psychologist who was helpful and he made a point of making contact with He is there if needs him and I have rung and met him on occasion to discuss state of mind.

missed most of third term and managed to make it to school three to four days a week in fourth term. During this time she was seeing a psychologist once a week until the mental health care plan ran out. Two points here are that the start time for school 8.30am, is not conducive to kids struggling to get to school for health reasons. The mental health care plan should be more flexible for teens with real problems and extended on the recommendation of the treating psychologist.

In got back to me about the genotyping for and although not complete the test did show that CYP2C19 enzyme function is negligible. This means that she is a poor metaboliser of certain medications, including many anti-depressants. The report from DNAdose said that this 'would explain the reported serotonergic toxicity symptoms and the akathisia'. asked if I would be interested in getting another sample DNAdose, to complete the test, and possibly testing our other daughter. Given the result we were happy to pay $250.00 to have our other daughter tested.

The final report from DNAdose for is included in this submission[1]. The results for showed a slightly reduced CPY2C19 function. The implications for , in particular, are profound with regards to a number of medications including pain relief. Unfortunately this is a new area of research which appears to be little understood in Australia; and the reactions of the medical staff looking after have been interesting. Most people have been interested but appear to lack the knowledge to really understand how these test results are to be interpreted or what the implications are for

In December told me she needed to see the doctor again and arrange another mental health care plan. was prescribed desvenlafaxine by the GP, as this was a suggested antidepressant on the DNAdose report. This time was started on a very low dose. After some internet research of my own I had some concerns. Like most other antidepressants, desvenlafaxine, is not suggested for teens or children. The Christmas period appeared to flow nicely as we did our trip to

[1] Appendix A

and waited the arrival of our puppy (therapy dog). In January went to the GP again and I was called in to be told that had tried to overdose the previous night on a cocktail of desvenlafaxine, nurofen and Panadol. I had no idea. We were back to hiding the medication. was also seeing a different psychologist and a new psychiatrist, both advised taking off the desvenlafaxine.

Concerned about , I wrote to She contacted me several weeks later explaining that she had been on annual leave but would be happy to meet and discuss what had been happening. and I met with and she suggested sending another saliva sample to an American firm, Genelex, to do further testing with a focus on 5-HTT a serotonin transporter. At a cost of AUS$1000.00 it appeared to be a good investment. During this meeting suggested that might also be on the high functioning end of the autism spectrum. is currently being assessed for this and it would appear that some aspects of behaviour support this diagnosis. For us as a family it has been a revelation and has found the idea to be life affirming. In treatment terms it explained why cognitive behavioural therapy and particularly mindfulness was a failure.

also suggested that she come off the desvenlafaxine; she also explained more about akathisia and the side effects of antidepressant medications. About a week later I was called up to our bathroom by by a text message. This time I found her on the bathroom floor with blood oozing from a slice across her wrist. She was still holding a small box cutter, which she had used to inflict the cut upon herself. Concerned about any damage done and infection, I took her off to the again. Another long wait, and another boot out the door after they put a clean dressing on the wound and gave her tetanus shot. The next day I found cut marks on her upper thigh.

Coming off the Prestiq was an uncomfortable experience for as she suffered horrendous night sweats. In all, it took three weeks of stepping down the dose and then a month before she began to feel better.

When the results came back from YouScript the report told us that has extremely poor serotonin transporter function. It states 'Caucasian patients with this genotype are predicted to have slower responses, decreased rates of depression remission and increased levels of adverse effects to SSRIs as compared to the normal genotype'.[2] The other results supported the DNAdose report.

This year appears to be more engaged with school and with us as a family. The puppy gave her a focus and the discussions we have had, and are still having about autism and medication have given her a better understanding of who she is. is now drug free and looking back the self-harm and suicide ideation was directly attributable to the antidepressants she was prescribed. During my interactions with the medical

[2] Appendix B, p.2.

profession, was the only person to raise the concept of adverse drug reactions.

The medication aspect of story was highlighted on when had her appendix out. She spent two hours in recovery instead of half an hour, as is usual. During this time she was given a dose of anti-nausea medication and started to exhibit akathisia. The anaesthetist said that he had researched genotype issue to work out what was safe to give her. Yet, on discharge the paediatric registrar only saw 'sertraline' on the medical records and gave me a script for panadeine forte for pain relief. Codeine is less effective for due to her poor CYP2D6 function.

In conclusion the points I wish to make are;

- **Antidepressants are handed out by general practitioners as a 'stop gap' without regard to the fact that people can have significant adverse reactions to them.**
- **More research should be done on teen brains and medication, with a view to a larger study on adverse reactions and genotyping. This would avoid kids being put on a path into mental health from which they can never escape, with endless rounds of different medications which rather than helping, chain them to a life of misery or result in suicide and self-harm.**
- **There is an absence of psychiatric care for teens and their families, particularly after hours.**
- **The is a profound unawareness in the medical profession surrounding the mental health side effects and mental health manifestations of akathisia; leaving patients experiencing these effects extremely vulnerable.**
- **Awareness of the link between high functioning autism and suicide needs to be raised. People think of autism in terms of visible exaggerated behaviours, yet many kids like have well hidden behaviours or difficulties. For social interactions at school are exhausting and she struggles with girly chit chat, hence most of her closest friends are boys. was bullied by girls in grade 4, and this added to a sense of isolation and difference that became anxiety and depression.**

My aim in writing this submission is to raise the awareness of the dangers of medication and to suggest that genotyping should be used as a guide prescribing medication. It is also to highlight the reality that teens from stable middle class families from particular postcodes should not be readily dismissed as just attention seeking. All teens deserve to be treated with respect and due consideration.

Without the assistance of I do not know if would still be with us.

A CLINICIAN'S VIEW:

I first met on a Saturday morning in . I was rostered on to cover medical patients for the day, at the Hospital. At the time I was on a Psychiatry rotation, and prior to this rotation I had been working in the hospital's Emergency Department. When I arrived in the emergency department that morning, one of the registrars in the Department mentioned they had heard of a 'case' overnight who I would 'probably be interested in'.

To provide some context: Two months previously, while working in the emergency department, I had given a talk to the emergency medicine trainees about my professional area of interest; Pharmacogenomics, personalised prescribing and adverse drugs reactions in people with altered drug metabolism profiles (attributable to their genotypes). The doctor who told me about that Saturday morning, said that she sounded 'just like one of the cases' that I had used in my presentation.

After some pondering as to the appropriateness of me possibly reviewing case, I decided to ask the psychiatric nurse on duty (known to me) whether they would mind if I had a chat. I introduced myself to was extremely drowsy and barely coherent. It was apparent to me from the brief history that most likely had been experiencing akathisia, secondary to her newly started medication, 'sertraline'. It also made sense that there was likely a 'genotype' variation at play as many hours after taking diazepam was still extremely somnolent. With the knowledge that both sertraline and diazepam are primarily metabolised by CYP2C19, one of the major drug metabolising enzyme systems in the liver, I was keen to establish genotype. agreed to the testing and I proceeded to take the samples and send them for testing.

A few weeks later I received DNA-Dose report. Her CYP2C19 genotype was, as I had suspected, that of a poor metaboliser; has two alleles that code for absolutely no 2C19 functioning. Unfortunately the original set of swabs sent did not contain adequate DNA to complete the testing on other Cytochrome P450 systems. I made contact with and explained the situation. agreed to send further swabs to the lab for the remaining part of the test and also agreed to test younger sister.

Eventually remaining genotype results from GenesFX/DNA-Dose were available. I provided these to with an explanation regarding what these results meant. I also loaded the report and an explanation for future treating practitioners onto the Hospital, Digital Medical Record system; ensuring that an "alert" was in place on file to ensure future doctors involved in her care would be made aware of her drug metabolising capabilities. I also included with this a list of commonly prescribed medications and their respective enzyme pathways to aid in decision making for future care that may need.

Following this, several months passed.

I returned from annual leave in mid When I checked my postal mail at work, I found a letter from expression great concern for and asking for advice regarding management. I agreed to meet with and and see if I could help.

When I met with told me that had been prescribed desvenlafaxine (Prestiq) and that it seemed to be causing similar problems to the sertraline. They told me about their experiences with the psychiatrists and as well as numerous emergency department attendances and her attempts at self-harm. Unlike when I first met on this occasion she was alert and able to communicate with me.

During discussions, I noticed that exhibits many features that I understand to be consistent with a diagnosis on the autism spectrum; particularly in higher functioning females on the spectrum. I have had significant involvement with people on the autism spectrum. I have worked with young adults and teenagers who are on the spectrum; teaching them social and communication skills.

I have read widely in the area, both personal accounts of living with autism, as well as other texts in the area. Finally, and most importantly, I have my own personal experience of what autism is, and can be like; I am autistic and very high functioning.

I raised the possibility of an autism spectrum disorder with I proceeded to further screen using the Autism Quotient test. She scored 41 out of 50. 80% of adults on the autism spectrum will score greater than 32 out of 50 (with only 2% of controls scoring above this). I proceeded to ask more questions about history and behaviour to establish if features consistent with the DSM-V diagnostic criteria for 'Autism Spectrum Disorder" were present. described a plethora of features consistent with this diagnosis; while some may be perceived to be inconsequential in isolation, the combination of features is highly suggestive.

My awareness of the above average prevalence of depression and anxiety in individuals on the autism spectrum led me to ask about her 'original' depressive symptoms that resulted in the GP prescribing sertraline. described the feelings of isolation and being misunderstood, commonly reported as 'drivers' for depression in those with autism. She also, rather alarmingly, told me that nobody had actually asked her the reasons behind why she had felt down. She stated everyone asked me about my symptoms and how they were affecting me; 'they asked me how severe they were' etc. "Nobody really identified why I felt awful".

I recommended that seek a formal autism diagnosis. I also arranged for further DNA to be sent to America to test a further 3 enzyme systems (CYP3A4, CYP3A5 and CYP1A2), as well as serotonin transporter. To assist in liaising with other professionals involved in assessing whether has autism, I also provided a report documenting the features of autism identified in history.

Prior to finishing that meeting I provided and with a plan for gradually decreasing the desvenlafaxine, until ceased. I also provided education on likely withdrawal effects/symptoms, and some advice and options for managing these. I asked to remain in contact and to call if she had any concerns. We agreed to meet again once genetic test results were back from the USA.

When further genotype results were available I caught up with and had been experiencing numerous predictable withdrawal symptoms with the gradually tapering desvenlafaxine dose, however her mood was improving and she appeared to be less agitated. and had also done more of their own research into autism spectrum disorders and advised me that they felt this accounted for much of history very well.

Eventually was able to completely stop the desvenlafaxine, and a few weeks after that she had experienced significant reduction in the adverse effects she experienced while on it; including, night sweats, akathisia, agitation, low mood, temperature dis-regulation, urges to self harm etc.

The importance of considering an individual's genetic make-up and previous drug reactions when prescribing was highlighted when had her appendix out. Following operation contacted me to tell me that was experiencing akathisia again. The nursing staff observed the physical manifestations of this side effect, while experienced both the physical and mental agitation. The medication responsible is one that commonly causes akathisia and I would have advised against giving someone with a history of akathisia. Compounding the overall risk of adverse reaction, this medication was given with multiple other interacting agents that rely on, and even inhibit, the same metabolic pathway. This medication was given despite file having alerts on it regarding her susceptibility to these medications. It appears that because had not already had an adverse reaction to this exact medication that it was not recognised as a risk, even though information available would allow practitioners to extrapolate that the risk of such an adverse reaction would be notable in an individual with her history.

While has encountered other physical health issues, I have seen her change from an teen appearing agitated and fighting the urge to self-harm, to a teen with insight into her own emotions and the things that 'make her tick'. She has developed, through reading, an understanding of the things that make some situations more difficult, and identified 'strategies' to help cope with these; non-pharmacological strategies: This is something that is important whether a teen is on the autism spectrum or not.

When approached me about contributing to this submission, I was keen to do so in order to highlight some very important issues all present in case. is not 'different' or more 'challenged' than the majority of other teenagers and shouldn't be considered an 'exception'.

As a doctor, I am glad to have been able to help and her family with this difficult time; however I feel greatly concerned that our current system does not provide solutions for , or accessible avenues for the identification of, the following issues highlighted by case.

As a doctor, I am aware how controversial it is to step-up and say that we aren't doing the best that we can for individuals as a profession. Some of the limitation in provision of 'good' care is due to limited resources; some is due to gaps in education surrounding important issues and sadly, some is due to a reluctance to accept new scientific information and change current practise. I believe that most doctors do act in a way that they feel will bring the best outcomes to their patients; however I do see areas where things can, and should, be improved.

I can only hope that my peers recognise my contributions to this submission as a genuine attempt to improve the care that we, the medical profession, provide to teenagers, children and young adults with mental health presentations. By no means is this meant to be an exercise in 'pointing the finger', but it would be negligent not to highlight the significant damage that can be done when these flaws in the system come together to impact on one individual.

THE ISSUES:

1) **Current model of psychiatric care for children and adolescents**
2) **Prescribing of anti-depressants to children, teens and young adults**
3) **Availability of psychology services to teens**
4) **Akathisia: An under-recognised adverse reaction to medications**
5) **Pharmacogenomics: Recognition, understanding and application of personalised prescribing that reflects the wide inter-individual variations in drug handling & understanding of relative enzyme loading**
6) **Recognition of autism spectrum disorders in girls and highly functioning individuals**
7) **Depression as a presenting feature of autism**

Current Model of Psychiatric Care:

The current model of psychiatric care does not cater appropriately for the needs of teens/youths. In this model there are inpatient and outpatient psychiatric services available through the public health system. There is a significant lack of adolescent mental health services available through the private sector, even in major metropolitan areas.

The public sector limits its services to those patients perceived to be most at risk, or most severe/troublesome in presentation. Accessing assessment and early intervention of teen mental health complaints through these services is usually limited to those who have had acute presentations to emergency departments or emergency mental health services; the severity of symptoms needs to reach 'crisis' point before the system recognises that these individuals are in need of assistance.

Following referral to public psychiatric adolescent and youth services, funding and support options are predominantly targeted at 'at risk' groups; individuals with low socio-economic backgrounds, family turmoil, indigenous or foreign heritage, drug and alcohol issues etc. Patients origination from 'middle-class' or 'wealthy' backgrounds, perceived to have 'resources' are often referred back into the community leaving GPs to try and source appropriate services and supports (which often do not exist) for these patients.

Even if an individual presents to the 'system' in 'crisis', services are focused predominantly on addressing individual crises rather than the broader issues resulting in the individual reaching that point. Assessment is focused on immediate risk assessment (which is important), but lacks in the identification of underlying causes for symptoms/behaviours/deterioration. Treatment is targeted at averting imminent crisis rather than instituting assessment and treatment that will result in long-term understanding and stability.

Once in the public psychiatric system, consistency of care is rare. For developing individuals such as teenagers and adolescents this is particularly dangerous giving the rapidly changing nature of their cognition and understanding of the world. There are also 'few' avenues for paediatric mental health patients and their families to receive a 'reassessment' or global assessment; once a diagnosis or label has been documented, it is 'worked' with almost unquestioningly by future clinicians assigned to patient's case for the sake of expediency and 'professional courtesy' (in the faculties of psychiatry is is considered almost insulting for a practitioner to question another practitioner's 'impression'/'diagnosis'; because psychiatry is lacking in formal diagnostic tests that demonstrate pathology in a quantitative and visible manner, much of what backs any one particular psychiatric diagnosis is the assessing practitioner's personal opinion of the situation (with the information they have available to them being grossly limited by time, training, and resource constraints).

Unlike 'general medicine', psychiatry is an area where a majority of individuals will leave an initial appointment with a specialist with some kind of 'diagnosis'; there is a reluctance to say 'I don't know' and leave the presenting patient without a label for their concerns. In other medical specialties practitioners are forced to say 'I don't know' more often, as the majority of diagnosis rely on the presence or absence of physical test results. Psychiatry's reliance on 'criteria'/'lists' that are grossly subjective to assess patients makes it possible for 'diagnoses' to be speculated/formulated before much information about the patient is available. Once again, pressure to be 'treating' what the patient is complaining of also contributes to the 'over-diagnosis' of pathology, versus the acknowledgement of distress as a normal part of life. A medical history targeted at identifying the presence of the specific criteria for depression could well identify these in someone who has those symptoms due to a variety of causes, if the practitioner fails to seek information regarding the aetiology of these symptoms, the patient could be inappropriately be labelled as 'clinically depressed' and important underlying causes and conditions missed.

SUMMARY:

- **The public and private sectors are inadequately resourced to address adolescent mental health issues effectively.**
- **The current model of care does not allow for adequate or thorough assessment of youth presenting with mental health problems.**
- **The public mental health system for teenagers is focused on 'target' or 'at risk' groups; to the degree that individuals not displaying these 'red-flags' are left with negligible support and intervention.**
- **Due to limitations of resources, the current system is focused on crisis management. There is an inadequate focus on long term identification and management of issues.**
- **Criteria based diagnoses in mental health result in 'over diagnosis' of pathology and under-recognition of 'normal' parts of life; including growing up and normal levels of distress experienced in response to various life events.**
- **Reviews/revisions/removals of diagnoses are inadequate. Once in the 'system' and labelled 'mentally unwell' it is hard for youths to leave the system.**
- **Diagnoses are made without adequate consideration of underlying condition that may be contributing to symptoms.**

Antidepressant Prescribing:

The prescription of anti-depressant medication in youths in increasing; and, in most cases, occurs prior to trialling psychological interventions. Medical practitioners are largely unaware of the adverse 'mental health' side effects that are relatively common in those taking psychotropic medications. While practitioners are trained to recognise 'physical' adverse reactions, the unawareness of of these 'mental health' mimicking side effects places those taking these medications at great risk: A presentation with worsening 'mental health' features following commencement of antidepressant medications will usually be attributed to 'worsening' of the patient's condition, and rarely will an 'adverse drug reaction' be considered as one of the differential diagnoses.

General practitioners are aware of the void in middle-level community mental health services available to teens. There are large delays in being able to access the few private services (psychology and other) that exist. Pressure to 'address' a patient's depression, or feel as though they are 'addressing' the problem can result in inappropriate prescribing of psychotropic medications (including antidepressants) to this vulnerable cohort.

Children, teenagers and young adults prescribed antidepressants have an increased risk of suicide. The United States' Food and Drug Administration (FDA) has clearly documented that the risk of suicide and self-harm is elevated in youths prescribed antidepressants (particularly non-selective and selective serotonin re-uptake inhibitors - eg. sertraline). This risk is particularly apparent in the first months of taking these substances. Information about this risk, and other serious medication side effects, is not widely taught or accepted in the medical community; partly due to the availability of this information being in isolated circles of practitioners with an interest in the area. The risk is significant and the FDA requires most of these medications to carry a black box warning regarding these risks. Too often prescriptions are written without adequate advice about the risk of these side effects having been provided. The perceived safety of these medications is misleading practitioners to under-advise and under-recognise the serious adverse effects they have. When these medications were first introduced to the market, they were praised as options for the treatment of depression due to their increased safety profile when taken in overdose (as suicide attempts) when compared to their predecessors.

Teenagers are still developing coping mechanisms, learning where they fit into the world, finding out who they are etc. Many find this process distressing and difficult. Many will experience transient (or persistent symptoms) identified as 'depression'. The prescription of pharmaceutical agents to alleviate these symptoms, in place of teaching cognitive skills to enable these young people to cope, is doing our future generations a disservice. Most children presenting to paediatric psychiatric facilities are prescribed psychotropic medications eventually. This often occurs before any formal assessment by a psychologist, or attempt at psychological interventions.

SUMMARY:

- **Prescribing of antidepressants to young people is increasing.**
- **Antidepressants and other psychotropic medications are often prescribed as a 'fall-back' when practitioners feel they need to 'treat' a patient but there is a long wait for non-pharmaceutical interventions.**
- **The medical community does not widely recognise the serious adverse mental health side effects that antidepressants cause (and these are not uncommon).**
- **It is already recognised that children, teenagers and young adults are at an increased risk of suicide and self-harm when taken anti-depressant medications, especially in the first months of treatment.**
- **Practitioners' perception that the newer antidepressants are safer than their predecessors means often inadequate caution regarding the possible adverse effects is provided to patients and their families when these medications are commenced.**
- **Antidepressant medications are being prescribed to teenagers experiencing distress associated with normal life events and changes, rather than equipping these youths with coping mechanisms. This is partly due to the over diagnosis of 'distress' as 'pathology'.**

Psychology Services:

There is a severe lack of 'ground level' psychology services available to teens. There are not enough clinical psychologists working with this cohort. As a result there are delays in people being able to access psychological input. Best clinical practise suggests psychological interventions prior to medication in most conditions. Delays in accessing psychology services place pressure on practitioners to prescribe prematurely and inappropriately. The community is not widely aware that private psychology services can be accessed on mental health care plans from GPs. The perception remains, that these services are expensive to the point of being inaccessible, unless you have some form of private health insurance. The cost barriers to psychology services need to be addressed; as good psychological intervention can actually save money through prevention of progression to worsening mental health symptoms etc that may require hospital assessment and admission.

SUMMARY:

- **There are not enough psychologists available in the community**
- **There are significant cost barriers to a large number of the community accessing psychology services**

Akathisia:

Akathisia is characterised by an internal sense of restlessness that can result in an inability to remain still. It is classically considered to be a side effect characterised only by the physical manifestations of this inner restlessness; including pacing, fidgeting and other body movements. In reality, akathisia is a complex disorder that presents with a range of symptoms (driven by this 'restlessness'). The presentation can vary and include irritability, agitation, restlessness, impulsivity, motor agitation/restlessness, hostility, aggression, insomnia, ruminating thoughts, suicidal ideation and actions, urges to self-harm and anxiety. People with akathisia can be driven to suicide and homicide as a result of their condition. Because medical practitioners are only taught to recognise akathisia in its most apparent form (ie. visualised movement) it is a grossly under-recognised and under-treated side effect. Akathisia is most commonly seen as side effect of antipsychotic medications. However, it has also commonly been observed as being caused by antidepressant medications.

The awareness in the medical profession of the varied presentations of akathisia is highly problematic. Patient's presenting with anything that deviates from the classically taught motor restlessness will on most occasions not be identified as having a medication side effect; this is true even when the symptoms start soon after commencing a new medication (ie. there is historical support for the presence of a drug reaction being possible). Those with predominant 'mental agitation' in the presentation are at extreme risk of being perceived as having worsening mental illness; for many, this results in the prescription of secondary psychotropic agents, or increased doses of the agent originally responsible for their akathisia.

Because there are not medically standardised scales for identifying the varied presentations of akathisia and differentiating akathisia from mental disturbance of another origin, identification of this adverse effect is reliant upon individual clinician experience and understanding. Identification is also reliant upon detailed history taking (particularly of pharmaceutical agents the patient is/has been taking).

SUMMARY:

- **Akathisia is a common side effect of antidepressants and antipsychotics.**
- **Akathisia is not limited to physical manifestations such a pacing; the restlessness also commonly presents as cognitive disturbance including agitation, anxiety, suicidality etc.**
- **Akathisia is under-recognised and acknowledged with most practitioners not realising the wide variations in presentation.**

- **There are no tools/scales available to the medical practitioner that provide a systematic way to differentiate cognitive presentations of akathisia from mental illness.**
- **Akathisia can lead people to suicide and self-harm.**
- **Akathisia is treatable: Both through removal of the causative agent and through administration of other medications (removal of the causative agent being the preference).**
- **Unrecognised akathisia is frequently treated as mental illness and sufferers prescribed more of the very medications that cause the condition; antipsychotics and antidepressants.**

Pharmacogenomics:

Most medications are metabolised by enzyme systems in the human liver (others are renal excreted or removed from the body via other mechanisms). There are multiple cytochrome (CYP) P450 enzyme systems in the liver; these are the systems involved in drug metabolism. Any individual's functional capability of a system is determine by their genotype. Each person receives one 'allele' from their mother and one 'allele' from their father.

Standard medication doses assume that people have two 'normally functioning' alleles in their genetic make-up; and no inhibition of the action of the enzyme system from other agents. In reality, some people have 'partially functioning' alleles, 'non-functioning' alleles, 'super-functional' alleles and normal alleles. The variation in metabolic capability is extremely varied due to genetic variations.

The 6 most important CYP P450 enzyme systems are CYP2D6, CYP2C9, CYP2C19, CYP3A4, CYP3A5 and CYP1A2. These 6 systems account for more than 90% of the metabolism of drugs via the liver. With advances in medical technology, we are able to assess people's DNA and assess their inborn drug metabolism capabilities. By running a test, once in a person's life, we can know the 'maximum' potential their body has for metabolising different medications.

Knowing a person's genotype can guide prescribing.

Medication side effects are more likely to occur in, and be more serious in, people with abnormal metabolism profiles due to their genetics. If a person can't metabolise via a certain enzyme pathway, the drug will rapidly accumulate and cause 'mild' toxicities (adverse effects). If a medication requires metabolism via the enzyme system in order to become pharmacologically active, a person with no metabolic capability in that pathway will not receive benefit from that medication. Similarly, some people metabolise medications too quickly via certain enzyme systems; this can lead to toxicities and poor drug effect.

Pharmacogenomics can guide prescribing for any one individual based on their genetic make-up. By doing this, more appropriate medications can be selected, side-effect risks are minimised, treatment outcomes are improved, and costs are saved in finding a good treatment solution without the 'trial and error' method often employed in medicine.

Antipsychotics and antidepressants are often metabolised by 2D6, 2C19, 1A2 and 3A4. These systems, particularly 2D6, have wide variation in functioning and limited capacity.

There is already substantial literature documenting the extremely heightened risk of notable adverse drug reactions in patients with 'poor metaboliser' genotypes taking various psychotropics. These patients not only do not receive the 'intended' benefit of the prescribed medications, but end up with secondary significant side effects; including akathisia.

In Australia, the practice of pharmacogenomics and personalised prescribing is limited to a handful of practitioners. In America pharmacogenomics is more widely employed. The cost benefit, alone, of prescribing with this extra knowledge of individual patients has been sufficient for the health insurance companies in the United States to agree to fund this testing in patients to minimise payment of ineffective treatments, and to minimise the cost of treating preventable adverse medication reactions.

Most psychiatrists are not open to hearing about the utility of pharmacogenomics. There is an overall mentality that 'we know what we're doing', and 'you just have to try different things until they work'.

Genotype results that code for 'metaboliser states' (metabolism capabilities) that vary from the norm are far from rare. For cytochrome 2D6, 30% or more of the population would be expected to deviate from the norm. The numbers for 2C19 and 2C9 are slightly less, but still greater than 10%. For 3A4 and 3A5 approximately 5% of the population will have a significant variation that may affect outcomes. These numbers are not negligible.

It is not just genetics that determines how well a person can metabolise medications. Other medications and agents can inhibit and induce enzyme systems; adding to the variation. While there is some awareness of the impact of inhibitors and induces amongst medical professionals, this recognition only appears with gross levels of inhibition and induction; practitioners do not consider that multiple mild inhibitors are the same as a single potent inhibitor. Even without genetic information, improvement in detailed analysis of medication profiles looking at the overall weight on individual enzyme systems will reduce adverse events and improve patient outcomes.

SUMMARY:

- **Genetic make-up determines whether individuals can metabolise certain medications.**
- **We can test the genetics of the drug metabolising systems of the liver and know whether someone has poor, intermediate, normal or hyper functioning of any enzyme system.**
- **People with altered genetic make-ups and therefore metaboliser statuses are at a much greater risk of adverse medication effects.**
- **Genotyping, and prescribing with this information can minimise adverse medication effects and provide effect treatment faster.**
- **A person's genetic make-up never changes and the testing only needs to be done once in a person's life; the information can then be used to make decisions about thousands of commonly prescribed medications.**

- **Drug metabolism enzyme systems can be induced or inhibited (most commonly inhibited) by pharmaceutical agents and other substances. These effects are as important as considering an individual's underlying genotype.**

- **Pharmacogenomics is in its infancy in Australia. Most practitioners have not heard of this developing aspect of prescribing: Among those who have, some are interested, most feel it is 'overly complicated' because it was not taught during their primary medical studies, others still are completely opposed to the integration of this knowledge into clinical practice.**

Recognising Autism:

Autism spectrum disorders are classified as 'developmental disorders'. They are characterised by social skill difficulties, communication difficulties and sensory processing issues. The medical profession is adept at identifying people with classical autism. Those with lower IQs, male gender, and difficulties with verbal communication are much more likely to be diagnosed as children. Higher functioning articulate individuals and females are at risk of not being identified.

The ability to communicate verbally will often preclude children from an early diagnosis as the diagnosis has to be made using the identification of less obtuse symptoms. Higher functioning individuals also become 'harder' to identify as they mature as often they are able to learn strategies that 'mask' their underlying difficulties; essentially they 'get by' in the community, but not without experiencing significantly larger amounts of stress in everyday life than the general population.

Their deficits in social skills cause isolation and feelings of 'not belonging' and not being understood. This coupled with communication difficulties, usually apparent in more complex situations, can preclude them from activities and opportunities they would otherwise desire. The difficulties they experience in understanding and expressing their emotions have a substantial impact on their daily quality of life; and unlike their lower-functioning counterparts these difficulties appear to go un-noticed as they 'seem' to be coping.

There is a large amount of literature that also addresses the differences in the presentation of autism in females: The most prominent difference being that females are less likely to present with behavioural problems, instead they are more likely to present with features such as 'anxiety' and 'depression'.

The tendency to 'say things how they are' in higher functioning people with autism puts them at risk of being accused of narcism and other pejorative traits. Similarly, the black-and-white/all-or-nothing thinking style of those on the spectrum can lead practitioners to inappropriately interpret these individuals as deliberately difficult in their behaviour; often resulting in mis-diagnoses of personality disorders.

The Autism Quotient Test (AQ Test), designed by Simon Baron-Cohen is a good screening tool for identifying higher functioning people who may be on the autism spectrum.

SUMMARY:

- **Autism is common; it affects approximately 1% of the population.**

- **Autism presentations are highly varied and awareness of the variations of presentation needs to increase in the medical profession.**

- **Practitioners should not assume that autism is identified in early childhood. For many individuals the diagnosis is delayed until the teenage years and young adulthood.**

- **Females, people with higher IQs and those who are articulate are most at risk of having a diagnosis of Autism missed as the diagnosis relies on identification of less clear deficits.**

- **With age, people on the autism spectrum can learn to mask their symptoms and therefore become less 'obvious': However, the masking of symptoms does not remove the underlying experience of autism, and often they are experiencing large amounts of 'hidden' stress.**

- **Underlying autism may not be apparent until the stressors placed on the individual exceed the capacity they have to mask their difficulties.**

- **Females present differently to males on the autism spectrum. They are more likely to present with mental illness presentations that are secondary to the difficulties their autism causes them. They are less likely to present due to overtly socially unacceptable behaviours.**

- **Medical practitioners, particularly psychiatrists, are not taught to recognise autism. It is an under considered differential diagnosis in those experiencing difficulty.**

- **The ability to speak in articulate manner does not mean someone with autism will be able to 'express' what they want to when giving a history; while words may be spoken, the meaning to the person with autism may be different to that of the person hearing those words.**

- **Autism can be screened for with the AQ test. This should be considered in the diagnostic workup of any teenager presenting with mental health or behavioural problems.**

Depression and Autism:

Due to the social isolation, perceived or real, often individuals on the autism spectrum experience depression. Difficulties in expression their thoughts and emotions can also contribute, as well as the sensory challenges that individuals with autism face. Teenagers on the autism spectrum are at particular risk as, out of all the life phases, this is the time when people are most focused on 'fitting in' and demonstrating that they 'belong in the world'; this is also the period where higher functioning individuals on the spectrum who have not been identified are most likely to realise within themselves that they are 'different'. This is because social activity changes from being centred around task orientated play activities to being focused on social interactions and relationships (areas that those on the spectrum struggle with).

The all-or-nothing and black and white thinking of those on the autism spectrum can make the experience of isolation even more intense; the perception that they do not belong is easily extended to a mental conclusion that 'all is lost and they may never belong/fit in'.

Self-harm and suicide attempts are not uncommon in teenagers and young adults on the autism spectrum. It would be appropriate for thorough screening for the presence of an undiagnosed autism spectrum disorder to be conducted on all youths presenting with these issues: High functioning autism is such that, without specific enquiry into the presence or absence of diagnostic features, it is an easily missed diagnosis.

Recurrent attempts at self-harm and suicide are also more likely to occur in those on the autism spectrum as often the development of emotion recognition and regulation skills is delayed (even though their progression through life stages and society's expectations are not).

SUMMARY:

- **Rates of depression, suicide and self-harm are higher in the autistic population than the rest of the community.**
- **Difficulties with communication, socialisation, sensory processing, emotion regulation and expression contribute to the increased presence of depression in this population.**
- **Depression/self-harm/suicide attempts are often the first 'presenting feature' in undiagnosed high-functioning individuals on the autism spectrum as they have reached a point where they cannot compensate for their difficulties.**
- **All teenagers and young adults presenting with suicidal and self-harming behaviours should be specifically screened to rule out an underlying autism spectrum disorder.**

Conclusion

Our aim in this submission is raise a number of key issues that we believe are overlooked by many in medical profession with regards to teen suicide and self-harm. **experience and her serendipitous meeting with is an illustration of where the medical profession can fail a teen and also where awareness and thinking outside the box can help a teen. Our concern is that teens, particularly girls, may be put on a path of unwarranted and potentially dangerous medication keeping them trapped within the mental health system that stops them from living a full and healthy life. Worse, it highlights that some teen suicides could well be the result of avoidable adverse drug reactions.**

Appendix A

DNAdose More informed prescribing

Pharmacogenomic Test Report

Healthscope ADVANCED PATHOLOGY

GenesFX

FINAL REPORT

PATIENT INFORMATION

Patient: [redacted]
DOB:
Address: [redacted]S,

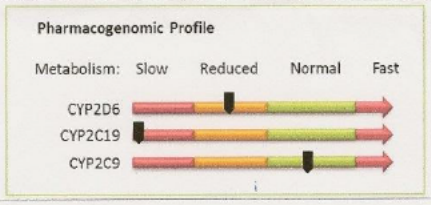
Ordered by:

INFORMATION PROVIDED FROM THE REQUEST FORM

Current Medications: Sertraline hydrochloride (Zoloft)

Clinical notes: Sertraline --> presented with serotonergic toxicity and akathisia symptoms on 50mg then 25mg of sertraline.

DNAdose Profile



Genotype Results

CYP2D6	***2/*5**	**Slightly Reduced**
CYP2C19	***2/*2**	**Slow**
CYP2C9	***1/*1**	**Normal**
VKORC1	**A/G**	**Increased Warfarin Sensitivity**

Legend: **Slow** = Poor Metaboliser, **Reduced** = Intermediate, **Slightly Reduced** = Heterozygous Extensive Metaboliser, **Normal** = Extensive (Normal) Metaboliser, **Slightly Increased** = Heterozygous Ultra-rapid, **Fast** = Ultra-rapid Metaboliser

CURRENT MEDICATION & SYMPTOMS

The CYP2C19 enzyme function is negligible (poor metaboliser) due to the presence of two non-functioning alleles. This result predicts a significant increase in the risk of side effects to sertraline in this individual. This result can explain the reported serotonergic toxicity symptoms and akathisia.

RECOMMENDATIONS FOR THERAPY

Based on the poor CYP2C19 metaboliser status, other CYP2C19 antidepressants are best avoided due to the increased risk of side effects. These include: citalopram, escitalopram, and moclobemide.

For an alternative antidepressant, consider desvenlafaxine, reboxetine, or agomelatine that are not metabolised by the enzymes tested.

The CYP2D6 enzyme function is reduced by 50% due to one normally functioning allele and a complete deletion of the other allele. Lower dosage of CYP2D6 dependent antidepressants could also be considered cautiously. These include, fluvoxamine and, fluoxetine.

The CYP2C9 enzyme function is normal due to the presence of two normal functioning alleles. This result predicts normal metabolism of CYP2C9 dependent medications, some of which are listed in the table below.

RECOMMENDATIONS FOR FUTURE MEDICATION

These results will have implications for 50% of the commonly prescribed medications. Some examples are listed below. For the complete list, visit www.genesfx.com.

[redacted]

WWW.GENESFX.COM
1300 GENESFX (1300 436 373)

Future Medications	Comment (side effects/non response)	Metabolism
Antidepressants: amitriptyline, doxepin, dothiepin and nortriptyline	An increased risk of side effects to some antidepressants due to a 50% reduction in CYP2D6 enzyme function	**Slightly Reduced**
Antidepressants: sertraline, escitalopram, citalopram and moclobemide **Benzodiazepines:** diazepam	A high risk of side effects due to negligible CYP2C19 enzyme function (poor metaboliser).	**Slow**
Antipsychotics: aripiprazole, chlorpromazine, haloperidol, risperidone, and zuclopenthixol	An increased risk of side effects to some antipsychotics due to a 50% reduction in CYP2D6 enzyme function	**Slightly Reduced**
Analgesics: codeine, oxycodone and tramadol	A possible reduction in the analgesic effect due to a 50% reduction in CYP2D6 enzyme function	**Slightly Reduced**
Antiplatelet: clopidogrel	A lack of antiplatelet effect is predicted due to the negligible CYP2C19 enzyme function (poor metaboliser). An increased risk of cardiovascular events and stroke from clopidogrel is predicted.	**Slow**
Anticoagulant: Warfarin	The VKORC1 enzyme profile is associated with some increased warfarin sensitivity due to one abnormal allele. However, when taken together with the normal CYP2C9 result the FDA recommends the following warfarin starting daily dose of 5-7 mg.	**Normal Warfarin Sensitivity**
Other CYP2C9 medications: most NSAIDs, phenytoin, and most sulfonylureas	Normal metabolism is predicted due to the normal CYP2C9 enzyme function	**Normal**
Other CYP2D6 medications: propranolol, metoclopramide and promethazine	An increased risk of side effects to other CYP2D6 dependent medications due to a 50% reduction in CYP2D6 enzyme function	**Slightly Reduced**

METABOLISM PROFILE

CYP2D6
This individual has reduced CYP2D6 enzyme function to 50% of normal function due to one normal functioning allele and one non-functional allele

CYP2C19
This individual has negligible CYP2C19 enzyme function (poor metaboliser) due to two non-functioning alleles

CYP2C9
This individual has normal CYP2C9 enzyme function due to two normal functioning alleles.

VKORC1

The VKORC1 enzyme profile is associated with some increased warfarin sensitivity due to one abnormal allele. However, when taken together with the normal CYP2C9 result the FDA recommends the following warfarin starting daily dose of 5-7 mg.

Note: For a complete list of CYP2D6, CYP2C19 and CYP2C9 dependent medications, please visit our website www.genesfx.com.

Note: Should you wish to discuss your patients results further you can speak directly with one of our pharmacogenomic experts by calling our GenesFX Health specialist support line 1300 436 373.

REPORT PREPARED BY:

Prepared by: GenesFX Health Pty Ltd - A/Prof Les Sheffield, Clinical Geneticist & Pathology Practitioner
Laboratory Results provided by: Healthscope Advanced Pathology (NATA accredited laboratory 3427)

Disclaimer: The pharmacogenomic test result in this report is just one factor that the prescribing doctor will take into consideration when determining a patient's appropriate medication and dose. These interpretations are being provided to the prescribing doctor as a tool to assist in the prescription of medication. Patients are advised not to alter the dose or stop any medications unless instructed by the doctor. The interpretation and clinical recommendations are based on the above results as reported by Healthscope Advanced Pathology and also uses information provided to GenesFX by the referring doctor. This report also assumes correct labelling of sample tubes and that the sample is from the above patient.

Appendix B

youScript

Personalized Prescribing Report

PATIENT:		RESULTS:			LAB INFO:
Patient:	[redacted]	Test:	Phenotype:	Genotype:	
DOB:		CYP2D6	Intermediate Metabolizer	*2/*5	
Acct:	Integre Health	CYP2C19	Poor Metabolizer	*2/*2	
Ref:		CYP2C9	Normal Metabolizer	*1/*1	
		VKORC1	Intermediate sensitivity to warfarin	G/A	
		CYP3A4	Normal Metabolizer	*1/*1	
		CYP3A5	Normal Metabolizer	*3/*3	
		5-HTT	Poor Serotonin Transporter	SA/SA	
		CYP1A2	Hyper Inducer	*1A/*1F	

Patient's genotype will never change.

Login to YouScript to identify possible interaction risks when making medication changes.

MEDICATIONS:

No medication list provided.

PRESCRIBING SUGGESTIONS:

Action	Drug Impacted	Type
n/a	n/a	n/a

Medication list needed to determine possible interactions.

Please login to YouScript (www.youscript.net) to add medications or call a YouScript Support Specialist at (877) 431-4362 for assistance.

LABORATORY RESULTS INTERPRETATION:

Laboratory Director: Teresa H. Aulinskas, Ph.D.

CYP2D6 Intermediate Metabolizers exhibit less than normal enzyme activity. Their genotype consists of either one active and one inactive, one partially active and one inactive, or two partially active CYP2D6 alleles. For CYP2D6 inactivated drugs, consider less than standard dosage to prevent adverse effects. For prodrugs that require activation by CYP2D6, consider increased dosage or an alternative treatment for optimal therapeutic response.

CYP2C19 Poor Metabolizers exhibit greatly decreased enzyme activity. Their genotype consists of two inactive CYP2C19 alleles. For CYP2C19 inactivated drugs, consider alternative treatments or less than standard dosage to prevent adverse effects. For prodrugs that require activation by CYP2C19, consider increased dosage or alternative treatment for optimal therapeutic response.

CYP2C9 Normal Metabolizers are the common phenotype for CYP2C9 enzyme activity. Their genotype consists of two fully active CYP2C9 alleles. May prescribe CYP2C9 metabolized drugs following standard dosing practices.

Patients with the **VKORC1** (-1639 GA) genotype exhibit **intermediate sensitivity to warfarin**. Results may be used for initial warfarin dose titration along with CYP2C9. Consult label or www.warfarindosing.org for dosing advice and adjust warfarin dose based on INR and concurrent medications.

CYP3A4 Normal Metabolizers are the common phenotype for CYP3A4 enzyme activity. Their genotype consists of two clinically active CYP3A4 alleles (absence of *22). Prescribe CYP3A4 metabolized drugs following standard dosing practices. Patients still have significant variation in CYP3A4 activity.

CYP3A5 Normal Metabolizers are the common phenotype for CYP3A5 enzyme activity. Their genotype consists of two severely reduced activity CYP3A5 alleles (*3). Prescribe CYP3A5 metabolized drugs following standard dosing practices. This phenotype may also be known as CYP3A5 non-expressors.

5-HTT (SLC6A4) **Poor Serotonin Transporters** have two reduced function alleles. The Long A (LA) and Extra Long A (XLA) alleles are reported to have increased expression compared to the Extra Long G (XLG), Long G (LG), Short A (SA) and Short G (SG) alleles. Caucasian patients with this genotype are predicted to have slower response, decreased rates of depression remission and increased levels of adverse effects to SSRIs as compared to the normal genotype. Consider both genotype results and ethnic variation when selecting applicability and interpretation of the results.

CYP1A2 Hyper Inducers exhibit increased enzyme induction in the presence of a CYP1A2 inducer. Their genotype consists of either one or two CYP1A2*1(F/J/L) alleles. If no CYP1A2 inducers are currently present, monitor for addition to the regimen of CYP1A2 inducers such as montelukast, phenytoin, phenobarbital, omeprazole, smoking, etc. In the presence of a CYP1A2 inducer, consider less than standard dosage compared to CYP1A2 normal inducers for CYP1A2 inactivated drugs to prevent adverse effects when co-administering with CYP1A2 inducers.

Laboratory Note:

Non-Genelex Test Results: CYP2D6, CYP2C19, CYP2C9, and VKORC1 testing was performed by Healthscope Advanced Pathology, Victoria, Australia on 09/20/2013. Healthscope Advanced Pathology tested for fewer genetic variations than the Genelex panel.

Legend:

Clinical Impact: Major Substantial Some Insignificant

Clinical Indication for Testing: Patient taking medicines metabolized by the cytochrome P450s or other enzymes, has a personal or family history of adverse reactions including treatment failure, or to confirm the presence or absence of relevant genotypes and as an aid to dosing and co-medication administration. DNA testing does not replace the need for clinical and therapeutic drug monitoring.

Methodologies: PCR based assays detect listed alleles, including all common and most rare variants with known clinical significance at analytical sensitivity and specificity >99%. Variants tested may include: **CYP2C19**: active *1; inactive *2, *3, *4, *5, *6, *7, *8, *12; partially active *9, *10; rapid *17. **CYP2D6**: active *1, *2; *2A, *35; inactive *3, *4, *5, *6, *7, *8, *10, *11, *12, *14, *15, *19, *20, *36; partially active *9, *17, *29, *41; gene duplications *1, *2, *4, *10, *41. **CYP2C9**: active *1; inactive *2, *3, *4, *5, *6, *8, *11, *13, *15. **VKORC1**: high sensitivity 1639G>A. **CYP3A4**: active *1; partially active *22. **CYP3A5**: active *1; inactive *3. Rare variants may not have been observed at Genelex. Other known variants not listed are not detected. Assays developed and performance characteristics determined by Genelex. **CYP1A2**: active *1A, *1E; decreased inducer *1C, *1K; hyper inducer *1F, *1J, *1L. CYP1A2 testing was performed at PGXL Laboratories, Louisville, KY. **5-HTT (SLC6A4)**: active LA, XLA; decreased SA, SG, LG, XLG.

Rare false negative or false positive results may occur. These tests have not been cleared or approved by the US Food and Drug Administration. FDA does not require these tests to go through premarket FDA review. These tests are used for clinical purposes and should not be regarded as investigational or for research. Genelex Corporation is accredited by the College of American Pathologists (CAP 1073709), certified under the Clinical Laboratory Improvement Amendments (CLIA No. 50D0980559), Washington State Medical Test Site No. MTS-3919, New York State Department of Health license no. PFI 8201 and is licensed to perform high complexity clinical testing in all US states.

Liability Disclaimer: This report is based solely on the medications and other information provided to Genelex and does not take all factors of the patient's care into account. Genelex is neither responsible or liable for the accuracy of the information supplied to Genelex by the treating healthcare professional. The treating healthcare professional has ultimate responsibility for all treatment decisions made with regard to the patient, including any made on the basis of the patient's genotype. Therefore, neither Genelex nor its employees, shall have any liability to any person or entity with regard to claims, loss, damage arising, or alleged to arise, directly or indirectly, from the use of information contained in this report.

References: Available at www.YouScript.com/healthcare-professionals or by request. Drug-gene tables with dosing considerations for commonly prescribed medicines can be accessed from the YouScript software at www.YouScript.net.

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