



Australian Government

Department of Health

Application Form

(New and Amended Requests for Public Funding)

(Version 2.5)

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires in order to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

The application form will be disseminated to professional bodies / organisations and consumer organisations that have will be identified in Part 5, and any additional groups that the Department deem should be consulted with. The application form, with relevant material can be redacted if requested by the Applicant.

Should you require any further assistance, departmental staff are available through the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

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Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): Australian Genomics Health Alliance

Corporation name: Murdoch Childrens Research Institute

ABN: 21 006 566 972

Business trading name: Murdoch Childrens Research Institute

Primary contact name: REDACTED

Primary contact numbers

Business: REDACTED

Mobile: REDACTED

Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers

Business: REDACTED

Mobile: REDACTED

Email: REDACTED

2. (a) Are you a consultant acting on behalf of an Applicant?

- Yes
 No

(b) If yes, what is the Applicant(s) name that you are acting on behalf of?

Insert relevant Applicant(s) name here.

3. (a) Are you a lobbyist acting on behalf of an Applicant?

- Yes
 No

(b) If yes, are you listed on the Register of Lobbyists?

- Yes
 No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

4. Application title

Genetic testing for childhood syndromes

5. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Children (<18 years) with the onset of clinical features/symptoms indicating a syndromic disorder in the first year of life, including a minimum of 2 of the 3 following indications: multiple congenital anomalies and/or dysmorphic facial features and/or moderate to profound cognitive impairment. Each particular genetic syndrome will have specific clinical features, depending on which organ systems are affected by the abnormal genes. The genetic basis of these conditions is highly heterogeneous, with a large number of genes (> 1000) implicated in genetic syndromes of childhood, making molecular diagnosis of these conditions complex.

6. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

Singleton next generation sequencing of coding regions in clinically affected individuals, delivered by NATA accredited diagnostic laboratories with appropriate accreditation (Massively parallel sequencing – full exome sequencing studies or genome sequencing studies).

While next generation sequencing has the ability to investigate all genes in the one test, only genes known to cause these syndromes will be analysed. A phenotype-driven list of candidate genes should be prioritised for analysis, followed by a broader scan of all other known genes with clinical evidence indicating possible involvement in the affected individual's condition.

Genes currently not known to be associated with syndromic disorders, or are unrelated to the clinical features being investigated, will be excluded from the analysis.

The suggested diagnostic test is agnostic of technology, and hence it is not prescriptive to the methodologies/equipment and reagents involved. For the purposes of this application the proposed test will be referred to as whole exome analysis (WEA) as investigation will be limited to the coding regions of the genome.

Cascade testing would also be required for relatives of affected individuals for whom a diagnosis was made via WEA. This would involve investigation of only the causative gene variant(s) found in the affected individual.

7. (a) Is this a request for MBS funding?

- Yes
 No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

- Amendment to existing MBS item(s)
 New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

Insert relevant MBS item numbers here

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

- i. An amendment to the way the service is clinically delivered under the existing item(s)
ii. An amendment to the patient population under the existing item(s)
iii. An amendment to the schedule fee of the existing item(s)

- iv. An amendment to the time and complexity of an existing item(s)
- v. Access to an existing item(s) by a different health practitioner group
- vi. Minor amendments to the item descriptor that does not affect how the service is delivered
- vii. An amendment to an existing specific single consultation item
- viii. An amendment to an existing global consultation item(s)
- ix. Other (please describe below):

Insert description of 'other' amendment here

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

- i. A new item which also seeks to allow access to the MBS for a specific health practitioner group
- ii. A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
- iii. A new item for a specific single consultation item
- iv. A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

- Yes
- No

(g) If yes, please advise:

Insert description of other public funding mechanism here

8. What is the type of service:

- Therapeutic medical service
- Investigative medical service
- Single consultation medical service
- Global consultation medical service
- Allied health service
- Co-dependent technology
- Hybrid health technology

9. For investigative services, advise the specific purpose of performing the service (which could be one or more of the following):

- i. To be used as a screening tool in asymptomatic populations
- ii. Assists in establishing a diagnosis in symptomatic patients
- iii. Provides information about prognosis
- iv. Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
- v. Monitors a patient over time to assess treatment response and guide subsequent treatment decisions
- vi. Is for genetic testing for heritable mutations in clinically affected individuals and, when also appropriate, in family members of those individuals who test positive for one or more relevant mutations (and thus for which the Clinical Utility Card proforma might apply)

10. Does your service rely on another medical product to achieve or to enhance its intended effect?

- Pharmaceutical / Biological
- Prosthesis or device
- No

11. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing? N/A

- Yes
- No

(b) If yes, please list the relevant PBS item code(s):

Insert PBS item code(s) here

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

- Yes (please provide PBAC submission item number below)
 No

Insert PBAC submission item number here

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Trade name: Insert trade name here

Generic name: Insert generic name here

12. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List? N/A

- Yes
 No

(b) If yes, please provide the following information (where relevant):

Billing code(s): Insert billing code(s) here

Trade name of prostheses: Insert trade name here

Clinical name of prostheses: Insert clinical name here

Other device components delivered as part of the service: Insert description of device components here

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

- Yes
 No

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

- Yes
 No

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

Insert sponsor and/or manufacturer name(s) here

13. Please identify any single and / or multi-use consumables delivered as part of the service?

Single use consumables: sequencing reagents

Multi-use consumables: N/A

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

The National Association of Testing Authorities (NATA) and the Royal College of Pathologists Australasia (RCPA) oversee the regulation of whole exome and whole genome sequencing for clinical purposes. Laboratories require accreditation by a joint NATA/RCPA process to ISO 15189, and specifically accredited to provide genetic testing via massively parallel sequencing with full whole exome analysis studies.

This accreditation process covers the technical aspects of the laboratory sequencing, analysis pipelines, curation (or interpretation) of results and production of the report to a clinical standard. This allows any accredited laboratory to provide equivalent WEA services to a minimum standard. There are no requirements for use of specific manufacturers reagents, equipment or analysis pipelines.

14. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: Insert description of single use consumables here

Manufacturer's name: Insert description of single use consumables here

Sponsor's name: Insert description of single use consumables here

(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

Class III

AIMD

N/A

15. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

Yes (If yes, please provide supporting documentation as an attachment to this application form)

No

(b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

Yes (if yes, please provide details below)

No

ARTG listing, registration or inclusion number: Insert ARTG number here

TGA approved indication(s), if applicable: Insert approved indication(s) here

TGA approved purpose(s), if applicable: Insert approved purpose(s) here

16. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

Yes (please provide details below)

No

Date of submission to TGA: Insert date of submission here

Estimated date by which TGA approval can be expected: Insert estimated date here

TGA Application ID: Insert TGA Application ID here

TGA approved indication(s), if applicable: If applicable, insert description of TGA approved indication(s) here

TGA approved purpose(s), if applicable: If applicable, insert description of TGA approved purpose(s) here

17. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

- Yes (please provide details below)
- No

Estimated date of submission to TGA: Insert date of submission here

Proposed indication(s), if applicable: If applicable, insert description of proposed indication(s)

Proposed purpose(s), if applicable: If applicable, insert description of proposed purpose(s) here

PART 4 – SUMMARY OF EVIDENCE

18. Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only). Please do not attach full text articles, this is just intended to be a summary.

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1.	Intervention (WES) in parallel to standard care	A prospective evaluation of whole-exome sequencing as a first tier molecular test in infants with suspected monogenic disorders	Singleton WES was performed in parallel with standard investigations. Of 80 enrolled infants, 46 received a molecular genetic diagnosis through singleton WES (57.5%) compared with 11 (13.75%) who underwent standard investigations. Clinical management changed following exome diagnosis 32.6% of diagnosed participants. Twelve relatives received a genetic diagnosis following cascade testing, and 28 couples were identified as being at high risk of recurrence in future pregnancies.	http://www.nature.com/gim/journal/v18/n11/full/gim20161a.html	3 March 2016
2.	Insert study design	Insert title	Insert description	Insert website link	Insert date
3.	Insert study design	Insert title	Insert description	Insert website link	Insert date
4.	Insert study design	Insert title	Insert description	Insert website link	Insert date
5.	Insert study design	Insert title	Insert description	Insert website link	Insert date

* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.

*** If the publication is a follow-up to an initial publication, please advise.

19. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). Please do not attach full text articles, this is just intended to be a summary.

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
1.	Intervention (WES) in parallel to standard care. Counterfactual health economic analysis.	Prospective comparison of the cost-effectiveness of clinical whole exome sequencing to usual care overwhelmingly supports early use and reimbursement	Follow on from study listed above. Cost data on diagnosis-related investigations and assessments were collected for a prospective, sequential clinical cohort of infants (n=40) who underwent singleton WES in parallel to usual diagnostic care. We determined costs per patient, costs per diagnosis and incremental cost per additional diagnosis for three alternative strategies for integrating WES into the diagnostic trajectory.	Draft as accepted for publication provided	Paper accepted and publication imminent.
2.	Intervention (WES) in parallel to standard care. Counterfactual health economic analysis.	Diagnostic impact and cost-effectiveness of exome sequencing for ambulant children with suspected monogenic conditions	Older cohort of above study. 44 children aged 2 years to 18 years with suspected childhood syndrome underwent singleton WES. Diagnosis was achieved in 52.3%. The diagnoses were unexpected in 37.8%, and clinical management was altered in 26.1%. Economic analyses of the diagnostic trajectory identified if WES were performed at first genetics appointment, there would be an incremental cost saving of AU\$5,461 (AU\$10,557, AU\$1,433) per additional diagnosis compared to standard diagnostic pathway.	Unpublished draft paper provided	Results available now, likely publication early 2017

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

****Date of when results will be made available (to the best of your knowledge).*

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

- 20. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):**

Royal College of Pathologists of Australasia (RCPA)
Royal Australasian College of Physicians (RACP)
Australian and New Zealand Child Neurology Society (ANZCNS)
Human Genetics Society of Australasia (HGSA)

- 21. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):**

As above

- 22. List the relevant consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):**

Rare Voices Australia (RVA)
Genetic Support Network Victoria (GSNV)
Syndromes Without a Name (SWAN)
Genetic and Rare Disease Network (GaRDN)
Genetic Alliance Australia
Australian Mitochondrial Disease Foundation (AMDF)

- 23. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:**

N/A

- 24. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):**

Name of expert 1: REDACTED
Telephone number(s): REDACTED
Email address: REDACTED
Justification of expertise: REDACTED

Name of expert 2: REDACTED
Telephone number(s): REDACTED
Email address: REDACTED
Justification of expertise: REDACTED

Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

PART 6 – POPULATION (AND PRIOR TESTS), INDICATION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

25. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:

Childhood syndromes are a clinically and genetically heterogeneous group of disorders, typically with onset in infancy or early childhood. Individual syndromes usually have a constellation of features including, but not limited to, facial dysmorphism, congenital malformations, single or multi-organ functional anomalies, and variable degrees of intellectual disability. They may be fatal in infancy or childhood, although survival into adulthood may be seen, and disease may be progressive or relatively static. For most there is no effective specific therapy but accurate diagnosis can optimise management including the institution of medical surveillance, commencement of treatments that can alter the natural history of the condition and avoidance of harmful medications. In addition establishing a genetic diagnosis has the potential to restore reproductive confidence in families.

26. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

Due to the heterogeneous nature of monogenic syndromes that present in early childhood, patients may present with a number of different clinical features as mentioned above.

Again due to the heterogeneous nature of these syndromes, patients may either present quite early on after birth (or may even be recognised in utero as a consequence of prenatal ultrasound or other imaging studies) with specific or nonspecific features, or manifest later in childhood following a period of normal development. Again these symptoms may be severe and the patients may present directly to hospital emergency departments, becoming inpatients, or they may be stable and be referred from the community for assessment by a paediatrician or specialist clinic.

A paediatrician will often first see these patients as inpatients or in a clinic by referral from a community general practitioner. After an initial clinical assessment the paediatrician is likely to refer the patient to one or more of the following specialists dependent upon the clinical presentation of the child: clinical genetics, neurology and/or metabolic medicine. A complete phenotypic assessment of the child is made with initial investigatory tests being carried out which may include the following: urine, blood and CSF biochemical studies, imaging of brain and/or other organs, muscle and/or liver biopsies for histological and functional studies, molecular karyotype analysis by microarray, and/or specific candidate gene testing based on the clinical phenotype. While some of these tests would continue to be required for initial investigative purposes and immediate clinical management of the patient, many would no longer be required if WEA was available. If a monogenic syndrome is highly suspected and the criteria for the test is met (see MBS item descriptor) an uninformative microarray would remain a requirement before proceeding to WEA.

After a clinical assessment, if a monogenic syndrome is suspected and a microarray has been returned with non-diagnostic findings, WEA would be considered as a diagnostic test.

27. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

As above – See Appendix 1 for current clinical management pathway.

PART 6b – INFORMATION ABOUT THE INTERVENTION

28. Describe the key components and clinical steps involved in delivering the proposed medical service:

The clinical pathway and requirements for these patients to be considered eligible for WEA is described as above. Once the request for WEA is made by the clinical geneticist, the patient would be required to provide a sample or consent to the access of a stored sample for use in the test.

Currently three diagnostic laboratories in Australia are accredited to deliver equivalent services of whole exome analysis for diagnostic purposes: SA Pathology, Victorian Clinical Genetics Services and GenomeOne (whole exome analysis by whole genome sequencing). It is expected that other diagnostic laboratories will become accredited to deliver equivalent services in the future.

The whole exome data would undergo detailed bioinformatic analysis, filtered based on a list of genes for which there is evidence of association with the phenotype under investigation. This gene list will be developed in consultation with clinical geneticists or other subspecialists.

As new disease genes are identified the gene lists will be expanded, allowing subsequent re-analysis of the initial whole exome data. Ideally, provision should be made available to permit re-analysis of the initial whole exome data at a future date.

29. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

No.

30. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

N/A

31. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

Whole exome analysis for childhood syndromes would be delivered as a one-off diagnostic test accessed through clinical geneticists, after multidisciplinary patient review. However, provision should be made for future re-analysis of the initial whole exome data in patients, for whom a genetic diagnosis is not established with the initial WEA, as new disease genes associated with the phenotype in question are identified. The frequency of this is suggested at 1-2 year intervals and only as clinically indicated, not as a regular interval-based occurrence.

32. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:

Consultation with paediatric subspecialists and/or clinical geneticists with expertise in genetic counselling (or access to a genetic counsellor) would be required at the time that WEA is initially offered to eligible patients. Again for the delivery of results to the patients' family, a formal consultation with the specialist, clinical geneticist and/or genetic counsellor would be required.

33. If applicable, advise which health professionals will primarily deliver the proposed service:

Paediatric sub-specialists and clinical geneticists would be required to discuss eligible patients with a multi-disciplinary patient review team led by a clinical geneticist to ensure patient suitability for the test.

A clinical geneticist would then be required to order the testing.

An appropriately qualified laboratory geneticist would be responsible for overseeing the WEA in the laboratory and providing the clinical report that would include interpretation of the results.

34. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

N/A

35. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

Only clinical geneticists would be able to request WEA, with appropriately qualified laboratory geneticist providing the service.

36. If applicable, advise what type of training or qualifications would be required to perform the proposed service as well as any accreditation requirements to support service delivery:

Clinical geneticists will have the appropriate formal qualifications as genetic specialists to make the request for WEA, and to provide guidance for the multi-disciplinary patient review meeting.

37. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select all relevant settings):

- Inpatient private hospital
- Inpatient public hospital
- Outpatient clinic
- Emergency Department
- Consulting rooms
- Day surgery centre
- Residential aged care facility
- Patient's home
- Laboratory
- Other – please specify below

Specify further details here

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

Inpatient private hospital – while this setting would not account for delivery of WEA for many of the patient population suggested, there is the possibility that patients may be seen in this setting, for example neonatal patients born in private hospitals.

Inpatient public hospital – these patients may present to the hospital with complex medical requirements requiring admission. This may be the first time that a genetic syndrome is suspected as the cause of their medical condition and the provision of whole exome analysis could be ordered while that patient is still under hospital care.

Outpatient clinics / consulting rooms – these patients may require regular monitoring by a number of different specialists with appointments occurring either in outpatient clinics or consulting rooms within both public and private settings. If at clinical review a monogenic syndrome is being considered, after a multidisciplinary review, this may be the setting in which the request for WEA is made.

38. Is the proposed medical service intended to be entirely rendered in Australia?

- Yes
- No – please specify below

Specify further details here

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

39. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

There is no direct comparator to the whole exome sequencing diagnostic test proposed. However ongoing review and use of health services can be considered as the comparator in the absence of a diagnosis.

In the absence of a diagnosis, children with suspected syndromes are regularly reviewed by multiple sub-specialists for diagnostic purposes. Where diagnostic testing is available and a diagnosis is made, this ongoing review and testing would be minimised or tailored to the diagnosis. In addition, in some cases a specific genetic diagnosis will point to specific therapies or surveillance measures based on known predictable health risks.

Where a definite clinical diagnosis cannot be made, it is often reflective of the incomplete and/or undifferentiated nature of the patient's initial presentation to specialist services. Traditionally these patients would be reviewed periodically in the hope that further phenotypic features would emerge over time to enable a diagnosis, or with new knowledge a genetic diagnosis becomes apparent. This approach may yield a diagnosis in a relatively short time, where clear phenotypic features develop relatively quickly, for example in Kabuki syndrome, where typical facial features of this syndrome are often present by 18 months of age. However, a patient presenting early in life with microcephaly and developmental delay, would be unlikely to gain a diagnosis of Cohen syndrome until much later as the diagnostic clinical features manifest in late childhood to early adolescence. Such an individual would be liable to multiple rounds of futile, expensive testing until a genetic diagnosis is established.

In undiagnosed children, ongoing review by clinical genetics services would be required for the amount of time that it took for definitive features to manifest in patients with suspected monogenic syndromes. This may also include the provision of further testing which could include the following:

- tissue biopsies for histology and functional studies*
- brain and other imaging*
- repeated rounds of blood, urine and or CSF collections for biochemical screening
- electrophysiological studies
- molecular karyotype (microarray analysis)
- single gene testing

* usually performed under general anaesthetic with potential adverse outcomes

Where a clinical diagnosis can be made but the molecular cause is genetically heterogeneous, there may be repeated genetic tests, with the most likely candidate gene being first screened, followed by sequential testing of other candidates over a period of time. In some cases this lack of molecular diagnosis can result in an incorrect clinical diagnosis persisting, with inaccurate information provided with regards to recurrence risks and missed opportunities with regards to specific therapies or disease surveillance.

40. Does the medical service that has been nominated as the comparator have an existing MBS item number(s)?

- Yes (please provide all relevant MBS item numbers below)
 No

Specify item number/s here

41. Define and summarise the current clinical management pathways that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards including health care resources):

See Appendix 1 for flow chart for comparison of traditional pathway vs WEA pathway.

As the comparator is considered ongoing periodic clinical review and further testing, the clinical management pathway would include ongoing diagnostic testing and symptom management as required by the clinical presentation of the patients. Without WEA a diagnosis may eventually be made by the standard practices of ongoing review and testing of patients with suspected monogenic syndromes, which eventually could lead to more directed treatment of these patients. However, our experience suggests that earlier implementation of WEA in the diagnostic pathway will not only lead to a firm genetic diagnosis in a greater proportion of cases than with the “traditional” diagnostic pathway, but will dramatically shorten the time to diagnosis, as well as the cumulative costs to reach that diagnosis.

42. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

- Yes
 No

(b) If yes, please outline the extent of which the current service/comparator is expected to be substituted:

Some basic investigations will still be required for immediate clinical management of these patients and also to enrich the population of patients that will go on to receive whole exome analysis. Some of these tests assist in ruling out the need for further genetic testing. One main test required prior to WEA would be microarray to rule out copy number changes (deletions or duplications) of genetic material. These changes are known causes of genetic conditions and cannot be adequately detected with existing whole exome sequencing. Other basic investigations could include the list provided in response to question 26, however this would be condition specific.

WEA would replace the need for some other tests in a number of patients including multiple sequential biochemical tests and individual genetic tests, gene panels, muscle and liver biopsies and repeat brain imaging.

For patients in whom no diagnosis is achieved through WEA there would be a decrease in the need for further genetic testing as majority of potential genetic causes of their disorder would be ruled out. However they would continue to be reviewed by specialist services, and potentially undergo other testing as their condition developed, as well as having the possibility of the original whole exome data being re-interrogated in the light of new disease gene discoveries in the future.

43. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service including variation in health care resources (Refer to Question 39 as baseline):

With the introduction of diagnostic whole exome analysis a molecular diagnosis may be made for these patients. In our study of infants with WEA in the population suggested in this application, 57% of patients achieved a diagnosis from WEA, compared to 13.7% receiving a diagnosis through the comparator pathway.

These diagnoses led to a change in clinical management for 32.6% of those patients that received a diagnosis: three patients had additional treatment started; one had unnecessary treatment stopped; and four had modifications to existing treatment regimens. Nine patients had additional surveillance for known complications of their conditions and one was released from surveillance based on an erroneous clinical diagnosis, which was corrected by the molecular diagnosis made via WEA.

Importantly, in four cases an initial genetic diagnosis was not established, but when the whole exome data was re-analysed a year later, four additional genetic diagnoses were made. This is one of the major advantages of whole exome analysis compared to static multi-gene panel based tests.

With the introduction of WEA, the diagnostic odyssey for 57% of these patients is shortened, decreasing utilisation of health care resources that would otherwise be required to maintain current clinical investigations and diagnostic processes.

Similar findings of clinical utility were noted in the study of WEA in the older cohort of childhood syndromes.

Cascade testing for relatives via Sanger sequencing of the individual gene involved:

Twelve relatives of the infants diagnosed by WEA received a genetic diagnosis following cascade testing (ie specific testing for the causative gene variant that had been identified), compared to only five that would have been diagnosed by standard care.

Twenty-eight couples were identified as being at high risk (25 to 50%) of recurrence in subsequent pregnancies, as a result of a WEA diagnosis for their child. Standard care would have identified 13 of these couples.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

44. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

The clinical claims of provision of WEA for this patient population include provision of a molecular diagnosis where there was none able to be made, a decreased time to diagnosis resulting in averted ongoing review and testing, potential for targeted treatment (where available), change in clinical management (including provision of appropriate ongoing disease surveillance or cessation of unnecessary disease surveillance) for a proportion of those diagnosed, and restoration of reproductive confidence through the capacity to provide more accurate genetic counselling.

Where a treatment was available the decline in the condition of two patients ceased, while the detection of the disorder in a younger sibling through cascade testing, allowed treatment to begin before onset of symptoms, which may well have averted the likely onset of disability due to the condition.

Compared to the standard care, provision of WEA, regardless of it resulting in a diagnosis or not, is unlikely to cause harm. While whole exome analysis may be able to detect unrelated genetic conditions such as risk of heritable cancer, the restriction placed that the analysis and reporting of genes should only be for those clinically indicated for the condition being investigated would minimise the risk of unintended findings and hence would minimise any harm that could come from this.

45. Please advise if the overall clinical claim is for:

- Superiority
 Non-inferiority

46. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Safety Outcomes:

Avoidance of adverse events due to invasive interventions including tissue biopsies, and MRI scans, most of which would require a general anaesthetic in the paediatric population.

Clinical Effectiveness Outcomes:

Clinical effectiveness outcomes will vary with the individual syndrome however examples of key health outcomes due to provision of WEA and a resulting diagnosis are:

Major

Change in clinical management – Provision of effective treatment to delay onset or halt progression of disorder, ineffective treatments ceased, modifications of current treatment regimens.

Improved surveillance of known complications of disorder, discharge from surveillance (for incorrect clinical diagnoses)

Restoration of reproductive confidence (cascade testing)

Minor

Quality of Life/Utility

Carroll and Downs and the HUI23 utility measures – child

AQoL8D – parent

Social and Economic Impacts

Relationship impacts - Dyadic adjustment scale

Social connectedness – Social provisions scale

Impact on family financial circumstances

These measures are captured through surveys of the childhood syndromes cohort referred to in evidence provided. Measurements include base line and 12 month follow up data – currently unpublished.

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

47. Estimate the prevalence and/or incidence of the proposed population:

Based on the numbers of this proposed population seen in at the Royal Childrens Hospital over the course of the study (~150/18months) it is projected that 200 new patients per year would be seen across Victoria.

The backlog of patients already being seen by clinical genetics services, who would also be eligible as part of this proposed population is approximately 500 in Victoria alone.

By extrapolation of these numbers on a population basis the expected national incidence would be: 800 patients per annum.

Again by extrapolation of these numbers on a population basis the expected national prevalence would be: 2000 patients.

48. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

The service of whole exome analysis would be a one off test delivered per patient.

The applicants suggest a second service related to this diagnostic test, which would include the periodic reanalysis of the patients sequencing data, where clinically indicated. The advantage of this use of technology able to cover the whole exome in comparison to panel based testing for genes is the ability to reanalyse the data, without having to repeat the sequencing, when further clinical information about either the patient or new disease genes becomes available.

The re-analysis of the sequencing data would only be considered if clinicians become aware of new genes with clinical evidence of potential involvement in the patients condition, or if changes in the child's condition suggest other possible candidate genes. Re-analysis would be considered in conjunction with clinical review, which would be every 1-2years, however it would not be an automatically triggered time-based re-analysis.

It is acknowledged that the population of patients eligible for the whole exome re-analysis service is different to the patient population indicated in this application for WEA, and this would need to be considered separately for clinical utility and cost effectiveness.

Cascade testing would also be a one-off single gene investigation for first degree relatives of the affected patient and where clinically indicated.

49. How many years would the proposed medical service(s) be required for the patient?

N/A

50. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

It is suggested that 1/3 of the backlog of currently eligible patients using clinical genetic services could be seen and offered WEA in the first year, along with the newly presenting populations for that year. Hence the projected number of patients utilising the service in the first year would be approximately 1450 patients (650 current and 800 new).

51. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:

In the first three years of WEA being available all newly presenting patients and the majority of the backlog of patients would be able to be seen. This would be a total proposed number of approximately 4400 patients nationally.

Risk of leakage would be considered nil due to:
targeted testing of a highly specific population
multidisciplinary patient review team led by a clinical geneticist
ordering restriction to clinical geneticists

PART 8 – COST INFORMATION

52. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

Currently 3 clinical diagnostic laboratories are providing accredited services that would be considered equivalent for the purposes of analysis of the coding region of the genome, for diagnosis of childhood syndromes:

Victorian Clinical Genetic Services

Overall cost of WEA from receipt of patient sample to clinical report produced is \$2400 (+cascade sequencing if required for variant interpretation)

Laboratory Sequencing (inc. sample preparation): \$1300

Analysis/Curation/Reporting: \$1100

Cascade testing of single variant*: \$200

Reanalysis of whole exome data:

Production of a negative report where there are no new findings: \$350

Production of a report requiring curation of new variants: \$650

SA Pathology

Overall cost of WEA from receipt of patient sample to clinical report produced varies from \$1900 - \$2300

Laboratory Sequencing (inc. sample preparation): \$1000

Analysis/Curation/Reporting: simple bioinformatics (<10 genes) \$900

Complex bioinformatics (>10 genes) \$1300

Cascade testing of single variant*: \$350

Reanalysis of whole exome data:

Production of a negative report where there are no new findings: \$350

Production of a report requiring curation of new variants: \$700

Genome.One

Overall cost of WEA from receipt of patient sample to clinical report produced is \$4100**

Laboratory Sequencing (inc. sample preparation): \$2200

Analysis/Curation/Reporting: \$1900

Cascade testing of single variant*: \$200

Reanalysis of whole exome data:

Production of a negative report where there are no new findings: \$400

Production of a report requiring curation of new variants: \$600

* A number of laboratories would be able to perform this service, when carried out separate to the WEA.

** Note: WEA based on whole genome sequencing includes CNV analysis

53. Specify how long the proposed medical service typically takes to perform:

Provision of WEA requires pre-test counselling for the patient and/or parent(s)/guardian(s) in this instance which can take from 30 min to 1hr of specialist or genetic counsellor time.

The turn around times for the WEA are currently 8-12 weeks, but this is likely to improve when the current bottleneck of bioinformatics/curation is appropriately resourced.

Delivery of the results to the patients' parent or guardian could require anywhere from 30min to an hour if a diagnosis is made and discussion of cascade testing is required. And again counselling may be required after delivery of cascade testing results.

Re-analysis of whole exome data would take between 6-8 weeks dependent upon the findings of the reanalysis (as above), with follow up counselling where a diagnosis is found.

54. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

Category 2 – Diagnostic Procedures and Investigations
<p>Proposed item descriptor:</p> <p><i>Affected Individuals:</i></p> <p>a) Characterisation of germline gene variants via whole exome analysis, from a phenotypically driven gene list present in the mendeliome, in a patient (<18 years old) with a strong suspicion of a monogenic syndrome based on the following criteria:</p> <p>onset of clinical features prenatally, in infancy or childhood, and a minimum of 2 of the following features dysmorphic facial appearance, and/or single or multiple congenital anomalies, and/or moderate to severe cognitive impairment</p> <p>b) Re-analysis of whole exome data for characterisation of new germline gene variants, related to the clinical phenotype, in a patient (<18 years old) with a strong suspicion of a monogenic syndrome based on the following criteria:</p> <p>onset of clinical features prenatally, in infancy or childhood, and a minimum of 2 of the following features dysmorphic facial appearance, and/or single or multiple congenital anomalies, and/or moderate to severe cognitive impairment</p> <p><i>Family members:</i></p> <p>Request by a specialist for the detection of a previously identified single gene variant, in a first degree relative of a patient with a known monogenic syndrome where previous genetic testing has detected the causative variant.</p> <p>Fee:</p> <p>Affected individual: \$2400</p> <p>Re-analysis of WEA (negative report):\$350</p> <p>Re-analysis of WEA (curation required):\$650</p> <p>Cascade testing of family members (single gene variant):\$200</p>

PART 9 – FEEDBACK

The Department is interested in your feedback.

55. How long did it take to complete the Application Form?

10 hours plus time for consultation with relevant stakeholders and review of document.

56. (a) Was the Application Form clear and easy to complete?

- Yes
 No

(b) If no, provide areas of concern:

57. (a) Are the associated Guidelines to the Application Form useful?

- Yes
 No

(b) If no, what areas did you find not to be useful?

58. (a) Is there any information that the Department should consider in the future relating to the questions within the Application Form that is not contained in the Application Form?

- Yes
 No

(b) If yes, please advise: