GenV measures selection principles

To guide choices and technical solutions ahead of Cohort 2020s

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Version: 2019-09-21 v1

The purpose of this Position Paper is to guide choices of measurement tools that will deliver GenV's content over the first five years (prioritising measures 0-2 years in the first instance). The Solutions Hub Epidemiology Team is leading this work in 2019-20, with input from the Solutions Hub's Focus Area and Method Core groups, and the Cohort 2020s, Bio Discovery and Data Innovation teams.

While this document mainly focuses on outcomes measurements, the principles also apply to exposure measures and recognises their overlap. It should be read in conjunction with 'GenV lifecourse frameworks'. This reviewed a number of lifecourse frameworks, from which two were selected to guide choices particularly of exposure constructs.

Context

Ultimately, no study can transcend what it measures and how well it does so. This applies both to observational and interventional studies. Thus, the scope and composition of measures across the lifecourse – whether collected by GenV or others - will come to define GenV's capabilities.

1. **GenV's measures must reflect its Purpose, Aims, and Principles.**
   - GenV's <u>primary purpose</u> is to create large, parallel whole-of-state birth and parent cohorts for discovery and interventional research
   - GenV <u>aims</u> to generate translatable evidence (prediction, prevention, treatments, services) to improve the future wellbeing and health of children and adults, and to reduce disease burden
   - GenV's <u>principles</u> are Collaboration, Inclusion, Sustainability, Enhancement, Systematised Processes and Value.

2. **As far as possible, GenV's measures will be accessed from existing data.**

GenV's very large size and principles (particularly its driving emphasis on inclusion and retention) precludes face-to-face or lengthy one-on-one contact. Thus, measurement may occur via:

   a. accessing existing linked datasets;
   b. accessing enhanced or new linked datasets;
   c. biosamples, whether GenV-collected or existing;
   d. new collection directly by GenV or by services.

Because (d) is likely to be restricted by tight time constraints, GenV will also put considerable effort into (a), (b) and (c) to maximise the data available to it.

Principles and Discussion

The Figure outlines GenV's process flows for measures prioritisation, selection and ultimate inclusion.

The Table then pulls the above together to outline broad criteria and principles that will guide GenV's selection of outcomes measures going forward.

These are followed by a discussion of the factors underlying the Figure and the Table.
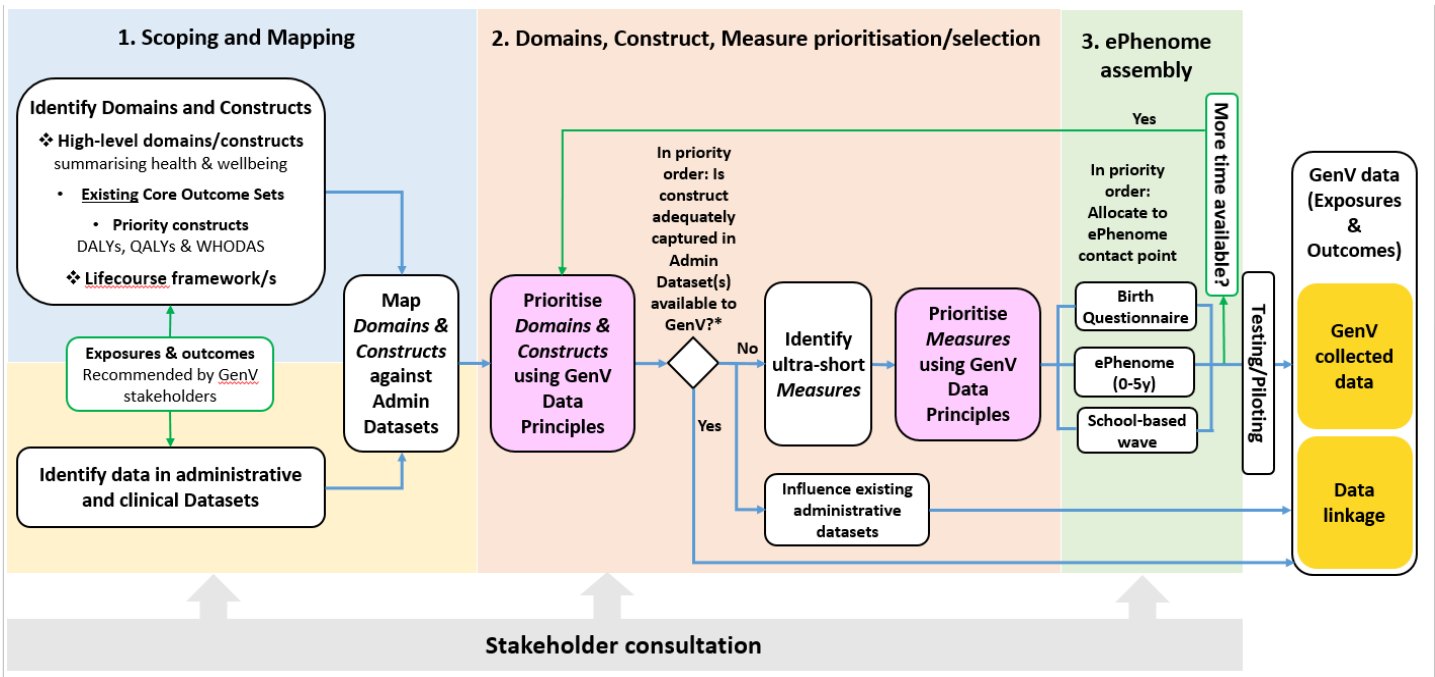

Figure: GenV measures prioritisation and selection process

Table: GenV outcome measures selection principles (0-5 years)

	Principles	Meaning in the context of measurement instruments
FILTER CRITERIA – only considered if meets these criteria		
1	**Meets GenV's Purpose and Aims**	Tools/constructs:
	Purpose: To create large, parallel whole-of-state birth and parent cohorts for discovery and interventional research	• Span the lifecourse • Are paired where possible across parents and children
	Aims: To generate evidence (prediction, prevention, treatments, services) to improve wellbeing/health and reduce disease burden	• Emphasise translatable outcomes prioritised for burden of disease, health and wellbeing
2	**Meets GenV Principles**	
	Collaborative	• Are developed via rigorous, standardised processes with families, individuals, providers • Are harmonised or complementary with major national & international initiatives
	Inclusive	• Apply to universal and targeted (eg clinical) populations • Cross ages (child + adult), gender, cultures, language, abilities and advantage
	Sustainable	• Are financially + technically sustainable within GenV; could be scalable beyond GenV
	Enhancing	• Are low-burden; where relevant, enhance parenting and/or services via meaningful feedback
	Systematised processes	• Combine into technically-feasible data waves via standardised, high-throughput processes
	Excellent	• Are accurate, reliable, high-resolution, valid, used internationally • When contributing to classifications, support use of logical agreed rules
3	**Meets Cohort 2020s practical constraints**	
	Targets 170,000 children born over 2 years + parents	Are capable of mass administration, with multiple waves administered simultaneously
	First GenV face-to-face assessment is not until age 6y	For 0-5y, must be deliverable digitally - remotely from GenV or administered by service providers
	Cohort 2020s commences Jan 2021; Vanguards from Apr 2020	Due to short time line, measures must already exist and be high quality
4	**Is not in universal datasets** of high quality, coverage, accessibility	MBS, PBS, VAED, VEMD, VPDC, SEHQ, NAPLAN, CDIS, others
5	**Is not available via multipurpose biomarker**	
TIMING		
6	**Provides a life map of key events**	Domicile change, diagnoses, illnesses, life events, treatments

	Principles	Meaning in the context of measurement instruments
7	**Provides a life map of overarching time-varying outcomes**	HRQL, physical health, mental health, body composition, pain, special needs, disability
8	**Optimises timing of overarching outcomes that are stable or track**	Neuro-cognitive, learning, senses, dysmorphism, social, fine + gross motor, physiology
PARSIMONY (the simplest & most frugal measures & explanations)		
9	**Data are multipurpose**	(eg facial images → emotion, symmetry, ethnicity, dysmorphism, eye gaze)
10	**Measures capture gradients** in the rawest form possible	Continuous data support multiple classifications of the same construct, eg hypertension, obesity
11	**Measures capture overarching relative health and wellbeing**	DALYs → Burden of Disease – includes diagnoses/conditions → ICD-11 classification
		Health status/HRQL/QALYs → cost-utility and cost-effectiveness
		Function & participation → ICF/ICF-CY classifications (WHODAS 2.0 or other mapping to this)
		Core Outcome Sets developed via rigorous multi-sectoral methods →GenV LifeCourse stages, Focus Areas
12	**Global and higher-order dimensions are prioritised** to measure multi-dimensional constructs	(eg Intelligence, 'g': dimensions - Verbal, Visual Spatial, Fluid Reasoning, WM, Processing Speed)
		(eg Mental health, 'p': dimensions - Internalising, Externalising, Thought Disorder)
13	**Innovative techniques directly measure phenotypic gradients**	Ultra-short adaptive tests, images, videos, web-based Apps as well as PROMs/PREMS
14	**Measures are meaningful to health**	Could change practice; have meaningful effect sizes, whether 'exposure' or 'outcome'

3. Measures collected by GenV must be parsimonious.

Given the constraints GenV faces, it follows that GenV-collected data will be characterised by brevity. For direct collection, there is no real alternative to brief digital measures, either pushed from GenV or collected via services. Any new collection by services is likely to pose significant challenges and require a major investment (see **section 8** below), so needs to be considered very carefully. It may be that brief, valid, digital measures do not exist for some constructs that are deemed important. In these instances, GenV may consult with experts to design new brief digital measures; explore whether options exist for 'depth' substudies to collect such constructs outside GenV; or accept that no one study can measure all constructs of interest and that attempts to do so have contributed to the failure of similarly-scaled studies. Fortunately, Australasia is rich in smaller birth cohorts,[1] as are other continents (eg ECHO, EU Lifecycle, UK CLOSER), many of which are readily accessible for addressing wide-ranging questions with specific foci.

4. GenV's outcome measures must be solution-focused.

Birth cohorts have traditionally focused on longitudinal associations. GenV's focus is on finding solutions to improve health and reduce burden of disease. This means that it must take a causal mindset, and be able to quantify potential health gain if feasible changes in putative causal factors were implemented. Testing such solutions may occur in a variety of ways – eg via trials within or outside GenV, quasi-experimental designs, simulation and causal modelling. All require robust outcome measures with agreement as to what constitutes meaningful success. An outcome is defined as all the possible results that may stem from exposures (defined in **section 5**).

To meet GenV's Aims, these must span:

- Generic measures that capture overarching relative health and wellbeing
  - Health-related quality of life (Quality-adjusted life years, QALYs)
  - Disease/disability burden (Disability-adjusted life years, DALYs), requiring information on conditions, illnesses and problems that parents and children experience (International Classification of Diseases 11th Revision, ICD-11)
  - Functional status (International classification of functioning, disability and health: children and youth version, ICF-CY framework)
- Core Outcome Sets (COS) tapping into major lifecourse outcomes – physical (body composition, dysmorphology, motor, growth, senses), mental, social, cognitive, learning, positive health
- Additional core outcomes important to GenV (eg driven by trials in the GenV window).

5. GenV's exposure measures must also be solution-focused.

For purposes of GenV, an 'exposure' is defined as an aspect of an individual's personal behaviour, lifestyle or experiences; inborn or inherited characteristics; environmental factors (social, economic, cultural, physical environments); and/or services/interventions in the health, education or other sectors that can plausibly contribute to the individual's outcomes. Any exposures measured by GenV must be judged highly relevant to GenV's solution focus. This definition considers 'confounders' and 'mediators' as within the remit of 'exposures'.

Which exposures and how best to measure them is less clear-cut. Potential exposures are essentially limitless and interest in specific exposures is often transient. Their effects are often small, their malleability limited, their measurement imprecise, and their time and/or equipment burden high.

Accuracy in some very important exposures (such as diet) remains effectively out of reach of brief measurement. Most importantly, unmeasured confounding and high degrees of collinearity mean that epidemiological associations that are plausible and robustly replicable are also often wrong. In some instances it has therefore been suggested that survey approaches be abandoned to make way for new mechanisms, eg biomarkers for micronutrients, alcohol and other substances. On the positive side, many exposures are already measured in existing universal datasets. Because exposures are often of high interest to services as well as families, more exposures could perhaps be implemented over the next decade via universal services for children born in the GenV window.

The document 'Lifecourse Frameworks GenV' provides two complementary frameworks to guide selection of exposure measures, which are not further considered separately from outcomes here.

6. GenV should prioritise data that are not available from other sources.

GenV will blend study-collected, study-enhanced (ie improvements/additions to existing datasets) and linked data. This document focuses predominantly on study-collected measures to capture high-priority constructs not available with high coverage, accessibility and quality in linked datasets.

7. GenV's measures should enable GenV's Focus Areas and Method Cores.

- Focus Areas:
  - Life course stages: Pregnancy, Newborns
  - Content: Development & Learning; Mental Health & Wellbeing; Healthy Environments; Organ Health; Obesity & Diabetes; Infection, Immunity & Allergy
  - Equity
- Method Cores: Population Health, Trials, Health Services Research, Registries, Geospatial, Place & Community, Digital Health, Bioresources (and others that may form in the future).

8. GenV data waves will be brief and digital.

GenV's very large size requires streamlined digital delivery to meet its principles. Face to face assessment by GenV itself does not appear to be an option until after school entry, for both cost and burden reasons.

GenV will directly push data collection waves to participants. Experience with large-scale digital PROMS and PREMS (Patient Reported Outcome/Experience Measures) indicate high completion that falls off steeply after about 3 minutes. We would expect such drop-off to be more pronounced among the participants GenV most wants to retain. This very short window could likely be extended if any additional time is highly engaging, valued, or relevant to individual participants. Pattern and extent of loss to follow-up is unknown; across the first 7 years of life, MOBA achieved 88%, 75%, 58% and 41% retention at ages 6 months, 18 months, 3 and 5 years[2] and DNBC achieved 92%, 70%, 66% and 57% retention at gestation 12 weeks, 6 months, 18 months and 7 years[3] relying on pen-and-paper questionnaires without face-to-face contact. GenV is aiming for higher retention, drawing on theory and burgeoning randomised evidence on what makes for effective digital engagement, habit formation and retention. This is the subject of a separate Position Paper led from the Solutions Hub Stream later in 2019 ('Review to guide GenV's digital engagement, completion & retention strategies'). Costs to GenV relate to (1) technical development and testing of a delivery vehicle and (2) manpower to manage research operations, dashboard and trouble-shooting (eg hot-line).

GenV will explore the potential for universal services (eg MCH nurses, 4yo kindergarten) to collect additional data items. This is yet to be scoped. Many factors will be considered, including (1) what measures would be relevant to the service, (2) whether these would include direct assessment or parent-completed survey or both, (3) the digital collection vehicle including a fail-safe mechanism to trigger entry to the measurement space, (4) equipment purchase, (5) building partnerships and agreements across the lead agencies and all 79 Local Government Areas, (6) developing and testing training materials, (7) training of service personnel at every wave, (8) quality monitoring and improvement activities, (9) loss to follow-up, (10) how to service any resulting care pathways, and (10) GenV's access to the data. In addition to the costs of (a) above, costs may need to be reimbursed on a per-child basis as well as for training and quality improvement.

9. Measures must be prioritised for low burden, potential for health gain, and validity.

Unfortunately, no single study can be all things to all people or all research goals. Therefore, choices must be made. GenV's aim to provide a framework for health services research, registries and health services research requires a large scale with high uptake and low attrition. In turn, this requires low burden, high-throughput measures that capture outcomes of wide relevance to parents, children, services and policy.

- **Duration of contact:** Implement short measurement sets comprising very brief measures
- **Overarching constructs:** Where evidence supports this, measure high-level constructs rather than their sub-components
- **Scientific validity:** Measures are supported by evidence of validity and reliability
- **Engagement:** Choose measures for interest, relevance, reward to participants, novelty, fun
- **Convenience**: Avoid measures needing visits, downloads, scenario set-up, extra hands, extra equipment, work by parent to return
- **Ease of items:** Choose measures with low cognitive load and fast response time
- **Enjoyment:** Minimise unpleasant, confronting, embarrassing items/measures
- **Direct benefit:** Provide feedback, belonging; may consider gifts, money/equivalents
- **Benefit to others:** Make the case for public good ie for other parents and children.
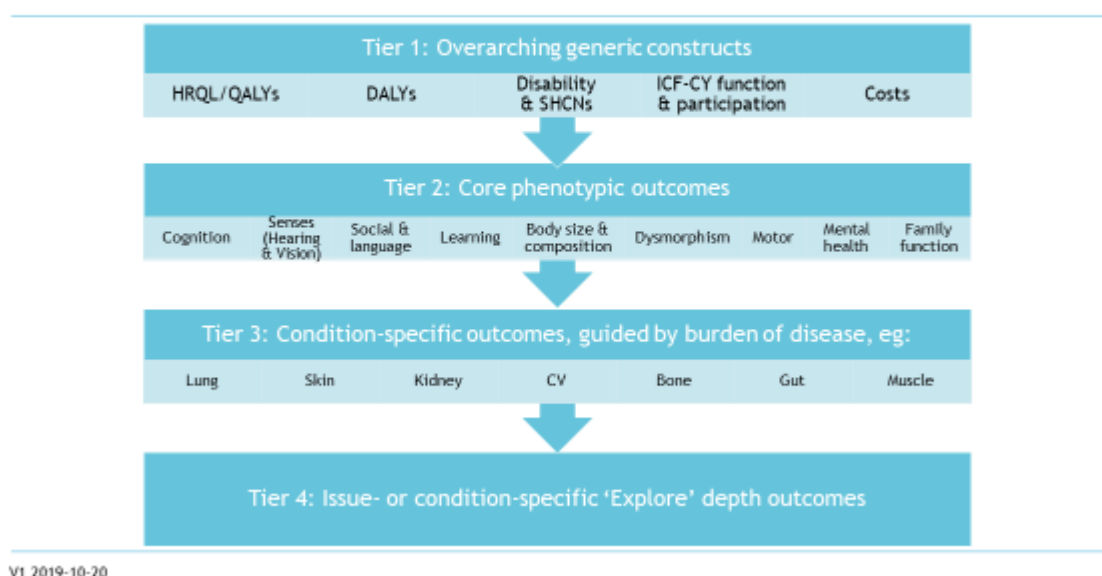
10. It's OK for GenV not to measure everything.

Even with these principles, choices will have to be made. More measures of interest exist than will be able to be fitted into GenV. This can be addressed by the following strategies:

- National Solutions Hub. As of 2019, all other 5 Australian states are simultaneously planning or implementing a new 'depth' discovery cohort of 10,000 participants. While these cohorts share common features with each other and with GenV, each has unique elements. Thus, wide-ranging questions will be addressed simultaneously throughout Australia in complementary breadth (GenV) and depth (other state cohorts) research. Via the proposed National Solutions Hub, GenV hopes to co-create a collaborative 'family' of these new studies with a culture of sharing of infrastructure, measures, resources and data.
- Expectations management. In all communication with stakeholders and future data holders, it will be clear that it is not feasible for GenV to measure every exposure and outcome of interest, and lengthy measures will be impracticable. Valid very short measures will be utilised to maximise the breadth of information captured in short, low-burden contacts with participants.
- Prioritisation of outcomes measures according to the following hierarchy.

GenV Outcomes Hierarchy

Tier 1: Overarching generic constructs				
HRQL/QALYs	DALYs	Disability & SHCNs	ICF-CY function & participation	Costs

Tier 2: Core phenotypic outcomes								
Cognition	Senses (Hearing & Vision)	Social & language	Learning	Body size & composition	Dysmorphism	Motor	Mental health	Family function

Tier 3: Condition-specific outcomes, guided by burden of disease, eg:						
Lung	Skin	Kidney	CV	Bone	Gut	Muscle

Tier 4: Issue- or condition-specific 'Explore' depth outcomes

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11. Conclusions

GenV is initially prioritising measures spanning 0-2 years, as well as broadly mapping measures for the full first 5 years of life.

The Cohort 2020s starts in January 2021 – measurement choices must be fast and pragmatic. GenV's Vanguard 1 (n≈2400 newborns) commences in April 2020, Vanguard 2 (n≈3500 newborns) in September 2020, and the main Cohort 2020s (targeting 170,000 newborns and their parents) in January 2021. It is anticipated that digital measurement waves will commence when infants are around 3 months of age. Allowing 3 months for ethical approval, the content of early measures must therefore be finalised as Vanguard 1 commences in April 2020. In practice, it needs to be earlier than this so that the technical delivery can also be developed, implemented and tested.

This document explores and summarises the principles that will enable GenV to make robust choices of outcome and exposure measures within its accelerated timeframe.

References

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