RESEARCH PAPER

Microsampling-Enabled Stress Biomarker Bioanalysis for Rural Maternal Autism Caregiving: A Critical Review and Development Framework

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Abstract

Background: Mothers of children with autism frequently sustain long-term caregiving work that overlaps with sleep disruption, service navigation, financial pressure, stigma and family role strain. These pressures may be intensified in rural agricultural communities, where specialist services are distant and household livelihoods depend on seasonal labour, transport, weather and income uncertainty. Objective: This critical review develops a framework for using microsampling-enabled stress biomarker bioanalysis as an access-supporting pathway for rural maternal mental health, not as a diagnostic substitute for clinical assessment. Review design: Targeted searches were conducted across health, psychology, rural health and bioanalytical literatures, with priority given to sources published from 2021 to June 2026 and to official bioanalytical guidance. Findings: A defensible programme requires three conditions: stress biomarkers must be interpreted longitudinally and contextually; DBS, VAMS, saliva and hair matrices require fit-for-purpose validation, matrix bridging and field-quality control; and biomarker feedback must be connected to tele-mental health, community health workers, autism-specific caregiver support and clear referral rules. Contribution: The framework positions microsampling as an access-support technology that becomes clinically and ethically meaningful only when embedded in contextual interpretation, maternal-centred feedback and rural referral pathways.

Keywords: autism spectrum disorder; maternal mental health; rural health; caregiver stress; stress biomarkers; microsampling; dried blood spot; volumetric absorptive microsampling

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1. Introduction

Autism spectrum disorder is a lifelong neurodevelopmental condition associated with heterogeneous patterns of communication, sensory processing, behaviour, learning and adaptive functioning. Recent public health updates underline the scale of the issue: the CDC reported that autism was identified in about 1 in 31 eight-year-old children in its 2022 surveillance data, while the WHO continues to frame autism support as a matter of access, dignity and lifelong care rather than a narrow diagnostic event (Centers for Disease Control and Prevention [CDC], 2025; World Health Organization [WHO], 2025). The Global Burden of Disease Study 2021 further confirms that autism contributes substantially to developmental and health-system burden across countries, although the lived consequences are distributed through families as much as through formal services (Global Burden of Disease Study 2021 Autism Spectrum Collaborators, 2025).

Mothers frequently remain the central coordinators of autism-related care. They

organise assessment, therapy, school communication, behaviour management, transport, family routines and financial decisions while also absorbing uncertainty about the child's future. Recent work documents high levels of caregiver burden, parenting stress, psychological distress and quality-of-life impairment among caregivers of children with autism, with mothers often reporting the heaviest emotional and practical load (Gentles et al., 2024; Herrero et al., 2024; van Niekerk et al., 2023; Wang et al., 2022). These difficulties are not reducible to individual coping style. They arise from repeated encounters with service scarcity, social judgement, child sleep disruption, behavioural crises and the practical work of keeping family life functioning.

Rural agricultural communities add a further layer of constraint. Mental health services may be geographically distant; public transport may be limited; broadband coverage can be unreliable; and small-community visibility may make help-seeking feel socially costly. Agricultural households also face seasonal workloads, weather uncertainty, pesticide and heat exposures, debt cycles, migrant labour conditions and income volatility (Becot et al., 2025; Henning-Smith et al., 2022; Keeney et al., 2023, 2025). Recent rural autism caregiver research similarly shows that resource scarcity, financial strain, emotional exhaustion, social isolation and support-system gaps are experienced together rather than as separate problems (Wan et al., 2026). For a mother caring for a child with autism, a clinic appointment is not only a health decision. It may require transport, child supervision, lost work time, negotiation with family members and willingness to be seen as someone who needs psychological help.

Malaysia and neighbouring Asian settings make this access problem particularly visible. Recent Malaysian work links problem behaviours in children with autism to caregiver burden in Kuching, Sarawak, and reports affiliate stigma, resilience and quality-of-life concerns among parents in Kelantan public hospitals (Chua et al., 2023; Salleh et al., 2024). These studies do not focus specifically on rural agricultural mothers, but they show that family stigma, service navigation and culturally situated support are not peripheral issues in Southeast Asian autism care. They strengthen the rationale for an access pathway that is technically credible while remaining locally acceptable.

Despite growing evidence on autism caregiver stress, rural mental health barriers and patient-centred microsampling, these literatures rarely meet. Caregiver studies often rely on psychological self-report without considering low-burden biological monitoring. Bioanalytical studies often validate sampling devices without addressing the routines of maternal caregiving. Rural telehealth studies often discuss access without incorporating physiological stress monitoring. This separation creates a translational gap: stress may be chronic, embodied and clinically relevant, but still remain invisible to rural support systems until a mother reaches crisis or disengages from care.

The central argument of this article is deliberately bounded. The review does not propose a universal biomarker model of caregiver mental health. It asks a narrower question: under which analytical, ethical and service-system conditions might microsampling become a low-burden access-support tool for rural mothers of children with autism? This boundary matters because biomarkers may make stress visible, but visibility has value only when it leads to interpretation, conversation and support.

This review asks: How can microsampling-enabled stress biomarker bioanalysis be developed into a credible and equitable mental health access pathway for mothers of children with autism in rural agricultural communities?

Figure 1 summarises the translational problem logic, beginning with autism caregiving demands and rural agricultural stressors and ending with biomarker-assisted monitoring linked to stepped care.

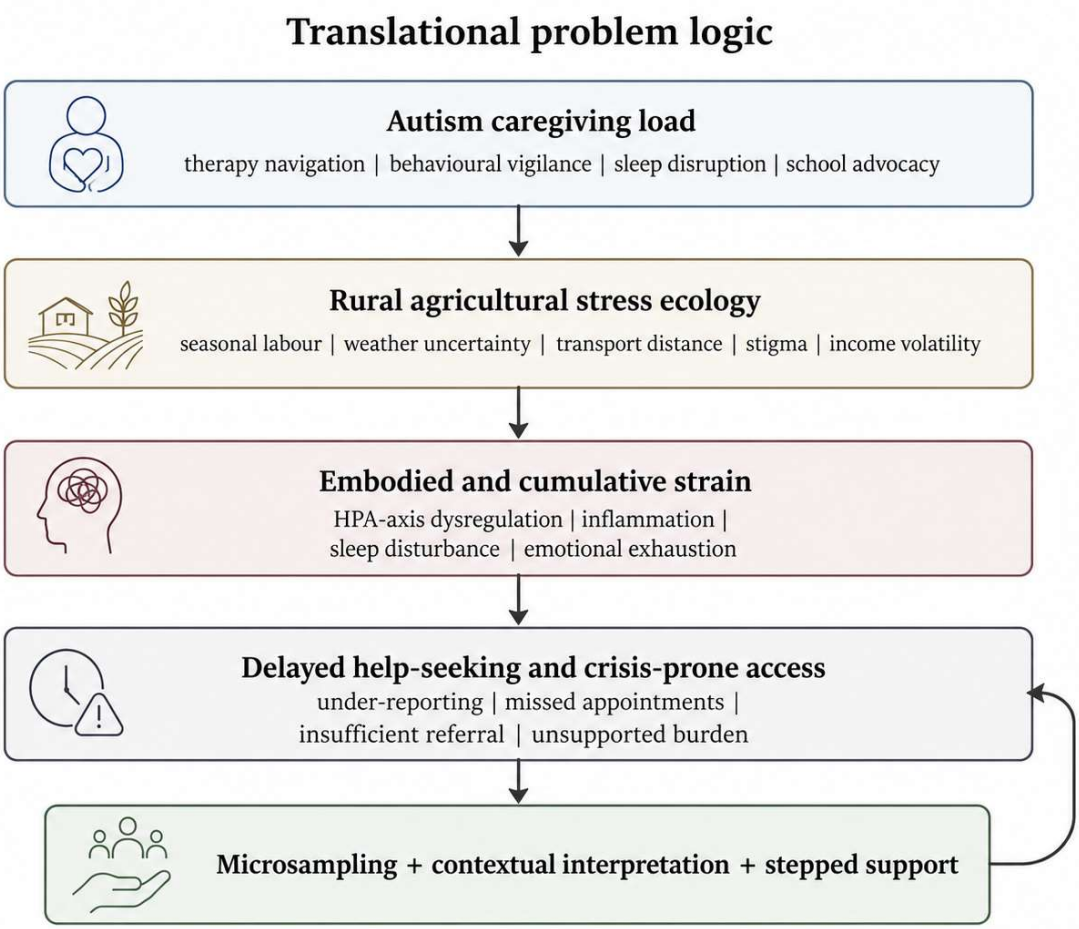

Figure 1. Translational problem logic linking autism caregiving, rural agricultural stressors and access delay.

Note. The model draws together autism caregiver stress, rural mental health access, rural autism caregiver and microsampling implementation literature (Ault et al., 2021; Becot et al., 2025; Gentles et al., 2024; Henning-Smith et al., 2022; Reed et al., 2024; Spooner et al., 2025; Wan et al., 2026).

2. Review Design and Synthesis Method

2.1 Review rationale

This article uses a critical integrative review design rather than a systematic review. That choice is methodological rather than rhetorical. The evidence base directly linking rural autism caregiving, maternal stress biomarkers and home-based microsampling is still emerging and fragmented. A systematic review would risk producing a narrow map of a literature that does not yet exist as a single field. A critical review is more appropriate because the task is to connect adjacent evidence streams, identify translational conditions and define a development agenda for empirical testing.

The review is therefore organised around the question of responsible development. It asks not simply whether microsampling can

measure stress biomarkers, but whether it can be designed in a way that is analytically valid, acceptable to mothers, useful to rural services and safe in ethical terms. This orientation follows recent calls to move minimally invasive biomarker work beyond laboratory feasibility and toward ecological, participant-centred interpretation (DeCaro & Helfrecht, 2022; Snodgrass et al., 2022; Spooner et al., 2025).

2.2 Search strategy and evidence synthesis

The review was informed by targeted searches last updated in June 2026 across PubMed, publisher databases, citation tracking through Web of Science-indexed and publisher-hosted records where accessible, Google Scholar, official regulatory/public health sources and journal reference chaining. Search terms combined four clusters: autism OR autistic children OR autism spectrum disorder; caregiver stress OR maternal mental health OR parenting stress OR caregiver burden; rural OR agricultural communities OR farmer mental health OR farmworker mental health; and microsampling OR dried blood spot OR volumetric absorptive microsampling OR saliva cortisol OR hair cortisol OR bioanalytical validation. Priority was given to peer-reviewed literature published from 2021 to June 2026, with older methodological or regulatory sources retained only when they remained necessary for bioanalytical validation or conceptual framing.

Sources were included when they contributed directly to one of four interpretive domains: maternal or family caregiving stress in autism; rural and agricultural mental health access; stress biomarker selection and interpretation; and microsampling, matrix validation, home collection or patient-centred sampling. Sources were excluded when they focused only on autism diagnosis biomarkers, animal biomarker studies, venous-only laboratory assays without remote-sampling relevance, or opinion papers that did not add a clear conceptual or implementation contribution. Evidence was synthesised narratively through a translational lens, with attention to feasibility, validity, acceptability, referral consequence and equity risk rather than pooled effect-size estimation.

Table 1 presents the evidence streams and the critical questions used during synthesis. This structure is intended to make the review logic transparent without claiming PRISMA-level systematic exhaustiveness.

For auditability, the synthesis followed an evidence-map logic rather than a PRISMA flow diagram. Each retained source was read for its contribution to one or more practical questions: who is at risk; what stress mechanism is plausible; which matrix can capture the signal; what validation is required before interpretation; and what care response follows from the result. The search was not designed to produce pooled estimates. It was designed to identify translationally relevant evidence across caregiver, rural health, bioanalytical and implementation literatures, and to test whether the proposed framework was supported by convergent findings across those domains. Because the review question crosses clinical, bioanalytical and implementation literatures, evidence was prioritised for relevance to framework development rather than ranked solely by study design.

Table 1. Evidence streams and critical questions guiding the review

Evidence stream	Core contribution	Critical question for this review	Illustrative sources
Autism caregiver stress	Documents parenting stress, family burden, service navigation and gendered caregiving work.	What forms of maternal stress remain hidden when rural mothers cannot easily access assessment or counselling?	Ault et al. (2021); Gentles et al. (2024); Herrero et al. (2024); Wang et al. (2022)

Evidence stream	Core contribution	Critical question for this review	Illustrative sources
Rural agricultural mental health	Explains transport barriers, stigma, workforce shortages, seasonal work and farm-related financial stress.	Which rural and agricultural conditions can distort both help-seeking and biomarker interpretation?	Becot et al. (2025); Henning-Smith et al. (2022); Keeney et al. (2023, 2025); Watanabe et al. (2023)
Stress biomarker interpretation	Clarifies HPA-axis, inflammatory and metabolic markers and their ecological confounders.	Which markers can support longitudinal risk formulation without becoming diagnostic labels?	DeCaro and Helfrecht (2022); Noushad et al. (2021); Robillard et al. (2024); van der Lubbe et al. (2026)
Microsampling and bioanalysis	Provides methods for low-volume, remote or home-compatible sample collection and validation.	What analytical and pre-analytical requirements must be satisfied before field use?	Bossi et al. (2024); ICH (2022); Reed et al. (2024); Thangavelu et al. (2023)
Implementation and stepped care	Links monitoring to telehealth, CHW navigation and referral pathways.	When does biomarker feedback become an access intervention rather than unsupported surveillance?	Adedipe and Walton (2025); Daniel and Maulik (2023); Gustafson and Torres (2024); Kaseje et al. (2024)

Note. HPA = hypothalamic-pituitary-adrenal; CHW = community health worker. The table defines the analytical boundary of the critical review rather than a systematic review extraction matrix.

2.3 Analytical boundary

The framework is limited to access-supporting stress monitoring. It does not propose biomarker testing as a substitute for psychiatric assessment, clinical interview or validated psychological scales. This boundary is important because cortisol, cortisone, C-reactive protein (CRP), cytokines and hair cortisol concentration are sensitive to sleep, infection, medication, body mass, endocrine status, pregnancy or lactation, menstrual status, heat, pesticide exposure and collection timing (DeCaro & Helfrecht, 2022; Noushad et al., 2021; Olthof et al., 2024; Stachanow et al., 2022).

Nor does the article assume that rural mothers primarily need additional monitoring. The clinical and ethical justification for microsampling lies in whether it makes support easier to reach, not whether it adds another layer of measurement. This distinction guides the remaining sections.

3. Stress Ecology of Rural Autism Caregiving

3.1 Autism caregiving as chronic relational labour

The stress experienced by mothers of children with autism is often chronic rather than episodic. Mothers may manage behavioural escalation, sensory distress, toileting or feeding difficulties, sleep disturbance, school exclusion, therapy appointments and family conflict while continuing paid or unpaid work. Recent qualitative analysis of caregiver stress shows that the burden includes both practical strain and a persistent need to anticipate risk, advocate for services and manage others' misunderstanding of autism (Gentles et al., 2024). Quantitative studies similarly associate child problem behaviours, low support and perceived burden with psychological distress and reduced quality of life among caregivers (Choi et al., 2023; Chua et al., 2023; Herrero et al., 2024; Rezq et al., 2025; Rusu et al., 2025; Wang et al., 2022).

In many households, this labour is gendered. Women are often expected to coordinate appointments, respond to crises and protect family routines. The result is not only emotional exhaustion but also a narrowing of time available for self-care, employment and help-seeking. Li et al. (2022), van Niekerk et al. (2023) and Herrero et al. (2024) emphasise that caregiver burden and parental self-efficacy are not minor side effects of autism care; they are clinically relevant family health issues. For rural mothers, the problem becomes sharper because professional support is less immediate and informal support may be informed by stigma rather than autism knowledge.

Evidence from Malaysia and other low- and middle-income settings reinforces this family-level interpretation. In Sarawak, caregiver burden was examined in relation to child problem behaviours, while Malaysian data from Kelantan foreground affiliate stigma and quality-of-life concerns among parents of children with autism (Chua et al., 2023; Salleh et al., 2024). LMIC caregiver-support reviews also show that stigma, poverty, transport and lack of trained services shape whether families can use interventions even when programmes are technically available (He et al., 2024). For the present framework, maternal stress is therefore treated as relational labour embedded in service systems rather than as an individual psychological deficit.

3.2 Rural and agricultural stressors

Rural agricultural communities should not be treated as generic rural settings. Service scarcity is intertwined with household labour, seasonal income, environmental exposure and small-community visibility. A mother may live far from autism specialists, mental health clinicians and laboratories. Even when telehealth is available, privacy at home, broadband reliability and digital confidence can constrain use. Agricultural calendars add another pressure: planting, harvest, livestock care and weather emergencies do not fit neatly around therapy or counselling appointments. These conditions are well described in rural telehealth, agricultural mental health and rural autism caregiver literature, where distance, workforce shortages, stigma, cost, seasonal demands and weak support networks repeatedly appear as access barriers (Butzner & Cuffee, 2021; Keeney et al., 2024; Wan et al., 2026; Watanabe et al., 2023).

Agricultural stress also complicates biomarker interpretation. Heat exposure, pesticide contact, injury, respiratory irritation, acute infection, disrupted sleep and physical labour may influence inflammatory or endocrine measures. These exposures are part of the stress ecology and should be recorded as core contextual variables. Table 2 summarises the main rural agricultural stressors that affect help-seeking and biomarker interpretation. A field diary should therefore treat agricultural workload, recent illness, medication, heat strain, pesticide exposure, sample-collection timing and major caregiving events as required covariates rather than optional descriptors.

Table 2. Rural agricultural stressors relevant to maternal stress monitoring

Stress domain	Examples in rural agricultural households	Likely effect on help-seeking	Implication for biomarker interpretation
Service geography	Long travel distance, limited specialist clinics, few autism-trained providers.	Delayed assessment, missed follow-up, reliance on informal advice.	Sampling must reduce travel and be paired with remote clinical review.
Agricultural calendar	Planting, harvest, livestock duties, weather-related emergencies.	Appointments are postponed during high-workload periods.	Sampling dates should record season, workload and sleep disruption.
Financial strain	Income volatility, debt, crop	Mental health care may be	Financial strain should be

Stress domain	Examples in rural agricultural households	Likely effect on help-seeking	Implication for biomarker interpretation
	loss, treatment cost, transport cost.	treated as less urgent than child therapy or farm survival.	measured as a contextual stressor, not treated as background noise.
Occupational exposure	Heat, pesticides, dust, injury, infection risk and physical fatigue.	Physical illness and exposure may reduce capacity to seek care.	Inflammatory markers require exposure and illness covariates.
Small-community visibility	Fear of being seen at a mental health clinic or judged by neighbours.	Under-reporting and avoidance of formal services.	Privacy-preserving feedback and contact preferences are essential.
Digital unevenness	Patchy broadband, shared devices, low digital literacy or limited private space.	Telehealth may improve access for some mothers but exclude others.	CHW support and non-digital options are needed.

Note. The table integrates rural telehealth, farmer mental health, farmworker mental health and rural autism caregiver evidence (Becot et al., 2025; Butzner & Cuffee, 2021; Henning-Smith et al., 2022; Keeney et al., 2023, 2025; Wan et al., 2026; Watanabe et al., 2023).

3.3 Why self-report is necessary but insufficient

Validated psychological scales remain indispensable. They capture distress, perceived stress, parenting burden, depression, anxiety, sleep and quality of life in ways that a biomarker cannot. Yet self-report can be constrained by stigma, literacy, emotional exhaustion and the normalisation of chronic caregiving strain. A mother may report that she is “fine” because distress has become routine or because acknowledging difficulty feels unsafe. Biomarkers may therefore add value when they are used as longitudinal signals that prompt supportive conversation rather than as labels imposed from outside.

The reverse error must also be avoided. Biomarkers do not speak for themselves. A single cortisol or CRP result cannot identify maternal depression, trauma or caregiving overload. The strongest design is multimodal: stress physiology, maternal report, child-related events, sleep, illness, medication and service access are interpreted together. Figure 2 presents this contextual interpretation model.

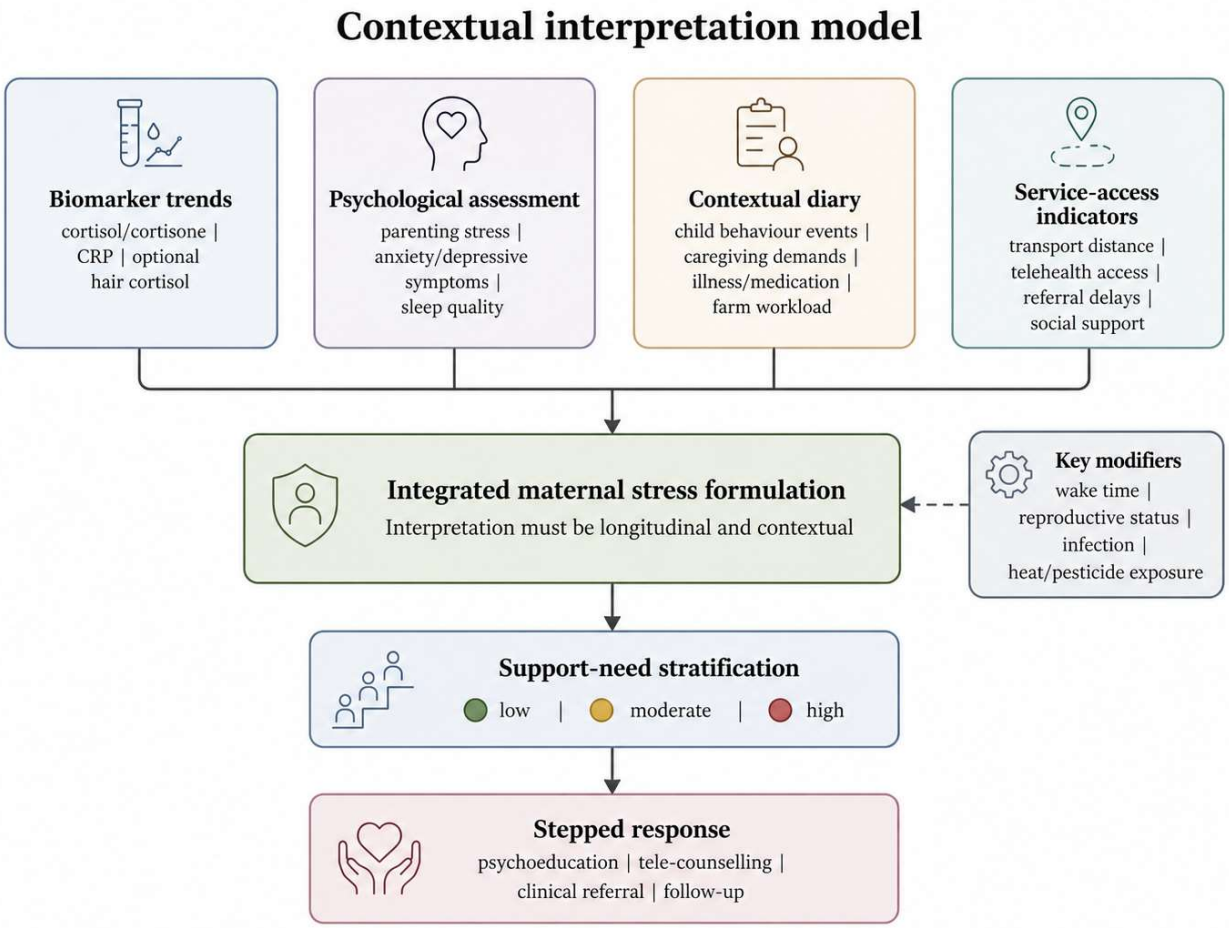

Figure 2. Contextual interpretation model for biomarker-assisted maternal stress formulation.

Note. Biomarkers are treated as one evidence layer among psychological, contextual and service-access data (Choi et al., 2023; DeCaro & Helfrecht, 2022; Gentles et al., 2024; Robillard et al., 2024).

4. Stress Biomarkers: Candidate Markers and Interpretation Rules

4.1 Biomarkers as longitudinal access signals

Stress biomarker work is attractive because it appears to offer objectivity. In caregiving contexts, however, objectivity is easily overstated. Cortisol, cortisone, DHEA-S, CRP, cytokines and hair cortisol concentration are measurable biological signals, but none is specific to autism caregiving or maternal mental disorder. They are best understood as access signals when repeated over time and interpreted with context.

A pragmatic rural programme should begin with a limited panel rather than a broad exploratory assay. Cortisol and cortisone are plausible first-tier markers because they relate to HPA-axis activity and can be measured in saliva or blood-derived matrices. CRP may be considered as a secondary inflammatory marker because DBS-based inflammatory assessment has become more feasible in remote research (Reed et al., 2024; Schwartz et al., 2025). Hair cortisol may help capture longer-term exposure, but hair practices, treatment, segment length and cultural

acceptability require careful handling (van der Lubbe et al., 2026). Table 3 proposes a staged panel.

Table 3. Staged biomarker panel for rural maternal stress research

Tier	Marker	Possible matrix	Primary interpretive use	Key cautions
Tier 1	Cortisol and cortisone	Saliva, DBS, VAMS, hair for longer-term exposure	HPA-axis rhythm and longitudinal stress load.	Strongly affected by collection time, sleep, steroid medication, endocrine status, illness and lactation.
Tier 1	Validated psychological scales	Questionnaire or interview	Clinical and psychosocial anchor for all biomarker interpretation.	Scale fatigue and under-reporting may occur in high-burden mothers.
Tier 2	DHEA-S	DBS, VAMS or venous reference subset	Adrenal counter-regulatory profile and stress adaptation research.	Age, endocrine status and assay differences complicate interpretation.
Tier 2	CRP	DBS, VAMS or serum/plasma reference subset	Low-grade inflammatory context and allostatic-load research.	Non-specific; affected by infection, injury, obesity, smoking, oral disease and farm exposures.
Tier 3	IL-6, TNF-alpha and other cytokines	DBS or plasma reference in tightly controlled sub-studies	Exploratory inflammatory phenotype research.	Low abundance, stability and assay variability require careful validation.
Tier 3	HbA1c, lipids or metabolic markers	DBS or VAMS	Broader maternal health integration in primary care settings.	Not specific to psychological stress; should not be framed as mental health markers.

Note. DBS = dried blood spot; VAMS = volumetric absorptive microsampling; CRP = C-reactive protein; DHEA-S = dehydroepiandrosterone sulfate. The staged panel draws on chronic stress biomarker and microsampling literature (DeCaro & Helfrecht, 2022; Noushad et al., 2021; Olthof et al., 2025; Reed et al., 2024; Schwartz et al., 2025; Stachanow et al., 2022).

4.2 Cortisol and cortisone

Cortisol is the best-known stress biomarker, but it is also one of the easiest to over-interpret. Salivary cortisol can characterise diurnal rhythm and awakening response; hair cortisol can approximate cumulative exposure; and dried blood matrices may support decentralised steroid measurement when appropriate LC-MS/MS methods and matrix bridging are in place. Recent DBS and VAMS steroid studies show that capillary or dried blood approaches can be analytically promising, but they also demonstrate why matrix, stability and concentration range matter (Olthof et al., 2024, 2025; Ponzetto et al., 2024; Stachanow et al., 2022; Tuma et al., 2024).

For maternal mental health access, the most defensible use is trend-based. A single "high" or "low" cortisol result should not be returned as evidence of abnormal coping. A repeated pattern, interpreted alongside sleep disruption, caregiver events and psychological scales, may justify supportive follow-up. Dutta et al. (2025) show that salivary cortisol can be used in maternal autism-related stress contexts, although such small intervention studies reinforce the need for cautious interpretation rather than immediate clinical generalisation.

4.3 Inflammatory and metabolic markers

Inflammation is relevant to chronic stress, but CRP and cytokines should be treated as contextual markers rather than mental health indicators. CRP is influenced by infection, obesity, smoking, injury, periodontal disease and physical exposures. Cytokines are analytically more fragile and may be more

sensitive to collection and storage conditions. In agricultural communities, heat, dust, pesticide contact, injury and infection may contribute to inflammatory variation. These variables must be recorded rather than treated as random noise.

Remote DBS collection for inflammatory markers has become increasingly feasible in population and psychosocial research, but feasibility in older adults or general community samples cannot be assumed to transfer directly to mothers of children with autism (Reed et al., 2024; Schwartz et al., 2025). Maternal caregiving schedules, child behaviour, household privacy and sample anxiety can affect completion rates and sample quality. For this reason, inflammatory markers should initially be secondary outcomes in feasibility and longitudinal studies.

4.4 Interpretation rules for responsible use

The minimum interpretation rules are therefore conservative. Cortisol or cortisone values should not be interpreted without wake time, collection time, sleep quality, medication history and recent illness. Inflammatory markers should be treated as allostatic-load context rather than direct psychological-distress indicators. Hair cortisol should be interpreted with hair treatment, segment length and cultural acceptability in view. DBS and VAMS results should be linked to matrix-specific validation rather than assumed to match serum, plasma or saliva. A biomarker result should be returned to participants only when three conditions are met: the assay has passed pre-specified quality criteria, the finding can be explained in non-diagnostic language, and a practical follow-up pathway is available. These rules protect mothers from unsupported labelling and protect researchers from false clinical claims.

The same caution applies to predictive modelling. Machine learning can identify patterns in caregiver stress data, but models trained on small, urban or socioeconomically narrow samples may produce misleading risk scores for rural agricultural mothers. Predictive modelling should therefore be introduced only after longitudinal data, explainable predictors and equity checks are available (Choi et al., 2023; Thaitumu et al., 2025).

5. Microsampling Technologies and Bioanalytical Requirements

5.1 Matrix choice

Microsampling is not one method but a family of collection approaches. DBS is familiar, inexpensive and logistically attractive, but it is vulnerable to spot-volume variation, haematocrit effects, punching variability, uneven drying and humidity damage. VAMS can improve fixed-volume collection, but device cost, extraction recovery and training requirements still matter. Saliva is less invasive and useful for diurnal cortisol, yet it is highly timing-sensitive. Hair can support longer-term cortisol research, but cosmetic treatment, washing frequency, segment length and cultural acceptability can affect interpretation. Recent microsampling reviews and metabolomics applications show increasing analytical potential, but they also underline that matrix choice should follow intended use, analyte stability and validation evidence rather than convenience alone (Bossi et al., 2024; Couacault et al., 2024; Protti et al., 2022; Roberts et al., 2022; Thangavelu et al., 2023).

Table 4 compares the most relevant matrices. In rural maternal autism caregiving, matrix choice should be guided less by laboratory convenience and more by the combined requirements of maternal burden, analyte stability, interpretability and referral consequence.

Table 4. Comparison of sampling matrices for rural maternal stress studies

Matrix	Strengths	Limitations	Best-fit use
Saliva	Non-invasive; feasible for repeated daily cortisol; acceptable for home use.	Timing sensitive; affected by food, oral health, contamination and missed samples.	Diurnal cortisol sub-studies and acute stress rhythm assessment.
Hair	Low transport burden; reflects longer-term cortisol exposure.	Hair treatment, cultural acceptability and segment length can bias interpretation.	Chronic stress sub-study when participants find hair sampling acceptable.
DBS	Low-volume finger prick; ambient transport; useful for some steroid, inflammatory and metabolic assays.	Haematocrit, spot volume, punching and drying variability require validation.	Larger rural cohorts after matrix bridging and home-use testing.
VAMS	Fixed-volume tips may reduce volume variability; compatible with LC-MS/MS workflows.	Device cost, underfilling, extraction recovery and storage effects must be evaluated.	Preferred blood microsampling option for steroid panels and repeated field sampling.
Venous reference sample	Established clinical matrix and broad analyte range.	Requires clinic or mobile phlebotomy; increases burden and transport needs.	Small validation subset for matrix bridging, not routine rural monitoring.
Contextual diary	Captures sleep, illness, medication, farm workload, child events and sampling time.	Reporting fatigue, literacy and missingness are possible.	Required companion measure for all biomarker interpretation.

Note. Matrix choice should follow intended use and validation evidence rather than convenience alone (Bossi et al., 2024; Couacault et al., 2024; Protti et al., 2022; Roberts et al., 2022; Spooner et al., 2025; Thangavelu et al., 2023).

5.2 Analytical validation and matrix bridging

A credible microsampling programme requires more than successful sample return. The analytical method must be fit for purpose and described with sufficient detail for replication. In line with the International Council for Harmonisation (ICH) M10 guideline and Food and Drug Administration (FDA) bioanalytical guidance, studies should report selectivity, carryover, calibration range, lower limit of quantification (LLOQ), accuracy, precision, recovery, matrix effect, dilution integrity, stability and quality-control procedures (FDA, 2024; ICH, 2022). For LC-MS/MS or LC-HRMS/MS steroid assays, internal standards, extraction procedures and acceptable criteria should be stated rather than implied. The proposed validation sequence is intended for research-use deployment; clinical deployment would require additional laboratory accreditation, regulatory review and clinical governance.

Matrix bridging is particularly important. Correlation between a microsample and a reference matrix is not sufficient to establish interchangeability. Bland-Altman analysis, concentration-dependent bias, limits of agreement and clinically relevant decision ranges should be reported. Recent DBS steroid work demonstrates why this caution matters: stability, capillary-venous differences and analyte-specific recovery can shape interpretation even when the same nominal biomarker is being measured (Olthof et al., 2024; Olthof et al., 2025; Tuma et al., 2024).

Figure 3 and Table 5 translate these standards into the proposed rural maternal stress context.

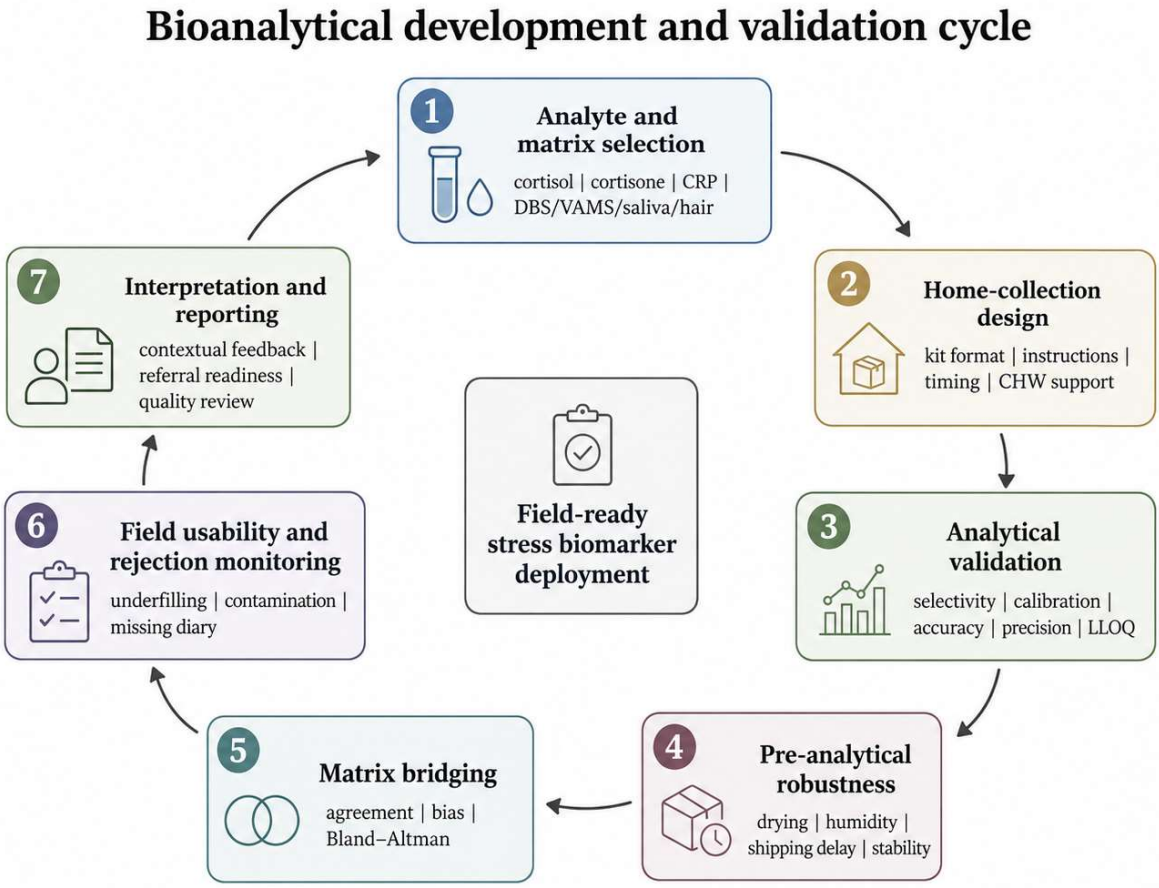

Figure 3. Bioanalytical development and validation cycle for microsampling-enabled stress biomarker work.

Note. The cycle separates assay selection, matrix bridging, stability testing, home-sample quality control, interpretation and field feedback. This is consistent with ICH M10 principles and recent microsampling reviews (Bossi et al., 2024; FDA, 2024; ICH, 2022; Thaitumu et al., 2025; Thangavelu et al., 2023).

Table 5. Minimum validation requirements before field interpretation

Requirement	What should be evaluated	Why it matters for rural maternal research
Selectivity and sensitivity	Interference, lower limit of quantification, endogenous background and assay range.	Stress markers may be low-abundance or affected by medication and endocrine status.
Accuracy and precision	Within-run and between-run performance using relevant QC levels.	Small biological changes should not be confused with analytical noise.
Recovery and matrix effect	Extraction efficiency and ion suppression/enhancement in DBS or VAMS extracts.	Dried matrices can behave differently from serum, plasma or saliva.
Haematocrit and volume effects	Blood spreading, device filling, spot quality and extraction across haematocrit ranges.	Finger-prick samples may vary with hydration, anaemia, device handling and field conditions.
Stability	Drying time, humidity, temperature, transport delay, freeze-thaw and long-term	Agricultural communities may face heat, distance and delayed mailing.

Requirement	What should be evaluated	Why it matters for rural maternal research
	storage.	
Matrix agreement	Bias, limits of agreement and concentration-dependent error against reference matrices.	Correlation alone does not establish that a microsample can replace a reference matrix.
Home-collection quality	Underfilled tips, layered spots, contamination, missing time stamps and rejected samples.	Pre-analytical error may be socially patterned by workload, literacy or privacy.
Result-reporting protocol	Plain-language feedback, thresholds for follow-up and referral documentation.	Mothers should receive support pathways, not unexplained biomarker labels.

Note. QC = quality control; LLOQ = lower limit of quantification. Validation requirements are adapted from ICH M10/FDA guidance and microsampling validation literature (FDA, 2024; ICH, 2022; Olthof et al., 2024; Olthof et al., 2025). Future studies should also report collection time, drying duration, storage temperature, shipping duration, humidity exposure, rejection criteria, haematocrit handling, calibration range, QC levels, LLOQ and matrix-bridging results.

5.3 Home-collection quality control

Home collection is often presented as simple. In practice, it transfers part of the pre-analytical process from trained staff to mothers who may be managing child distress, sibling care, household work or farm duties at the same time. Protocols should therefore be short, pictorial and forgiving. Sample quality problems should be categorised rather than reported only as a total rejection rate, because underfilled VAMS tips, layered DBS spots, insufficient drying, humidity damage, delayed return and missing contextual diaries point to different training and implementation failures. Each rejection category should trigger a specific corrective response, such as revised pictorial instructions, CHW-assisted demonstration, desiccant changes or simplified diary prompts.

A field-ready kit should include pictorial instructions, a short demonstration video, lancets or saliva devices, labelled collection cards or tips, desiccant, a humidity indicator, pre-paid return packaging, a brief contextual diary and a telephone or messaging support option. The diary should record collection time, waking time, sleep, illness, medication, menstrual or lactation status where relevant, child behavioural events, farm workload and pesticide or heat exposure. These details are not administrative extras; they are part of the assay interpretation pathway.

6. Six-Phase Development Framework

The framework proposed here is intentionally phased. Moving directly from laboratory feasibility to large-scale screening would be premature and ethically weak. Each phase has a decision gate: analytical fitness, maternal acceptability, sample quality, added interpretive value, referral capacity and equity. Figure 4 presents the overall development sequence, while Table 6 translates it into research designs and outcomes.

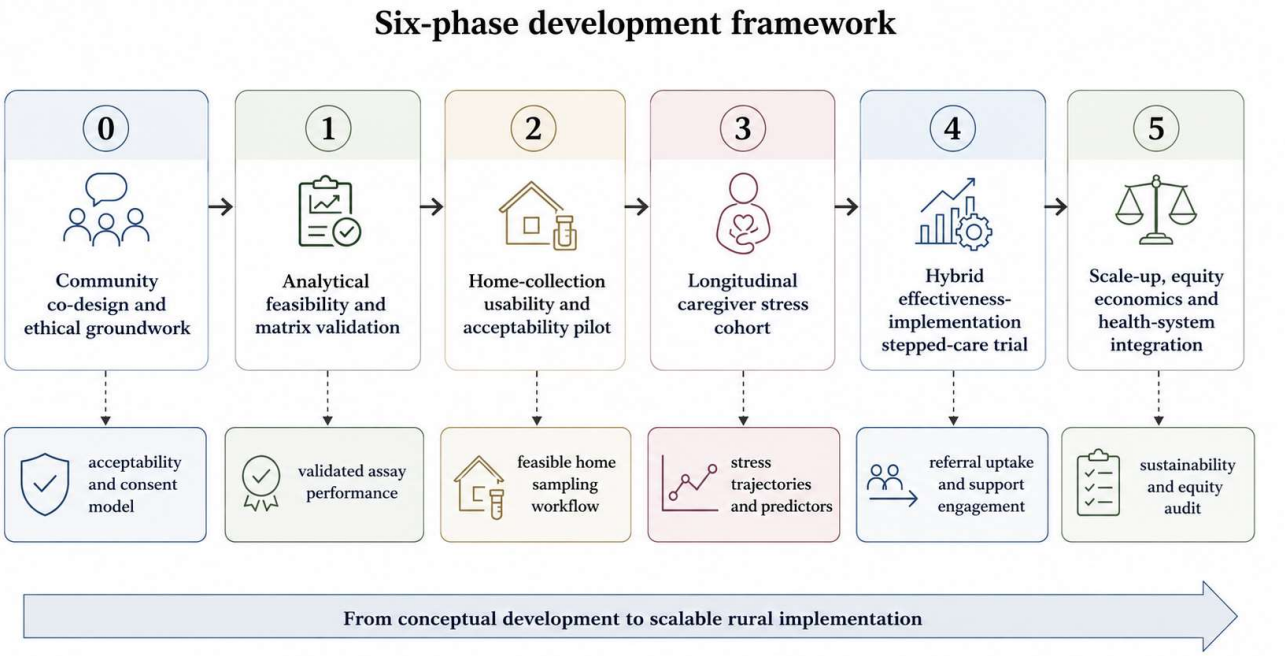

Figure 4. Six-phase development framework for microsampling-enabled maternal mental health access.

Note. The sequence moves from co-design to validation, usability, longitudinal modelling, hybrid implementation and scale-up evaluation. It draws on patient-centred sampling, CHW system integration and caregiver-support intervention evidence (Bossi et al., 2024; Gustafson & Torres, 2024; Kaseje et al., 2024; Reed et al., 2024; Shrestha et al., 2024; Spooner et al., 2025).

Table 6. Operational research plan for phased development

Phase	Aim	Suggested design	Primary outcomes	Go/no-go criterion
0. Co-design	Define acceptable language, sampling routes, privacy safeguards and feedback preferences.	Focus groups or interviews with mothers, CHWs, rural clinicians, autism providers and community leaders.	Perceived acceptability, stigma risk, preferred contact mode, result-return preferences.	Mothers view the programme as supportive rather than surveillant.
1. Analytical validation	Establish assay and matrix fitness for candidate markers.	Paired venous, DBS/VAMS, saliva or hair samples; controlled stability and matrix-effect testing.	Accuracy, precision, recovery, stability, LLOQ, limits of agreement.	Performance meets pre-specified research-use criteria.
2. Usability pilot	Test whether mothers can complete sampling under real caregiving conditions.	Small field pilot with CHW-assisted and self-collection arms.	Return rate, rejection rate, pain, time burden, confidence, willingness to repeat.	Sampling is feasible without excessive burden or high rejection.
3. Longitudinal cohort	Model stress trajectories and contextual modifiers.	Repeated measures over 6-12 months across agricultural seasons and school/therapy transitions.	Trajectory classes, biomarker-scale concordance, missingness, contextual moderators.	Biomarker trends add information beyond self-report alone.
4. Hybrid effectiveness-implementation trial	Test biomarker-assisted stepped care under real referral conditions.	Hybrid effectiveness-implementation study comparing enhanced usual care with biomarker-assisted access support.	Referral uptake, counselling engagement, distress reduction, implementation fidelity, adverse feedback effects.	Monitoring improves timely support without increasing stigma, anxiety or unsupported disclosure.
5. Scale-up and equity audit	Assess sustainability, cost, workforce load and equity.	Multi-site pragmatic implementation study in rural agricultural regions.	Cost per mother reached, reach by income/digital access, CHW workload, referral completion.	Benefits justify cost and do not widen inequities.

Note. CHW = community health worker. The staged design separates analytical validity, clinical utility and implementation effectiveness, which prevents premature clinical claims and supports realistic health-system integration (FDA, 2024; ICH, 2022; Kaseje et al., 2024; Shrestha et al., 2024; Spooner et al., 2025). Clinical service deployment would require additional laboratory accreditation, governance procedures and jurisdiction-specific regulatory review.

6.1 Phase 0: Community co-design

Phase 0 should occur before the first sample is collected. Rural mothers should be asked how they understand stress, what language feels non-judgemental, where sample collection would be acceptable, how results should be returned and which forms of support would be usable. Co-design should also include autism service providers, rural clinicians, CHWs or family navigators, agricultural community representatives and laboratory staff. A protocol designed without mothers may be efficient on paper but unworkable in daily caregiving life.

This phase should produce consent language, a result-return script, privacy safeguards, a referral directory and a decision rule for urgent risk. It should also clarify whether sample collection is home-based, school-linked, clinic-linked, mobile-outreach-based or CHW-assisted.

6.2 Phases 1 and 2: Validation before expansion

Phases 1 and 2 should remain small and disciplined. Phase 1 determines whether the proposed markers can be measured reliably under conditions that resemble rural transport. Phase 2 determines whether mothers can and will use the kit. These questions are related but not identical. A technically valid assay can fail because the collection instructions are confusing. A popular collection kit can still fail if the assay is unstable at high humidity or if VAMS tips are underfilled.

Field pilots should report rejected samples rather than quietly removing them. Rejection patterns may reveal who is being excluded: mothers with low literacy, heavy farm workload, low privacy, needle anxiety or limited phone access. Such data are not operational embarrassment; they are central to equity evaluation.

6.3 Phases 3 to 5: From trajectories to systems

Phase 3 should test whether longitudinal biomarker patterns add value to psychological scales and diaries. Agricultural season, school transitions, therapy disruptions and child behavioural change should be modelled as time-varying exposures. Phase 4 should then use a hybrid effectiveness-implementation design to ask whether feedback linked to stepped support changes help-seeking, referral completion or maternal distress. Phase 5 should evaluate whether the model can be sustained beyond research funding.

This staged logic is essential because an access pathway is only as strong as its weakest link. If a mother completes sampling but cannot access counselling, the intervention has failed. If the laboratory produces reliable data but feedback increases anxiety, the intervention has caused harm. If telehealth works only for mothers with stable broadband, the programme may reproduce inequity.

7. Implementation Pathway and Stepped Care

Implementation should begin with a practical principle: returned results require an available response. Mothers should not receive biomarker information without understandable explanation and a route to support. Figure 5 proposes a stepped-care pathway that links biomarker-assisted risk formulation to psychoeducation, peer support, caregiver training, tele-counselling, CHW follow-up and clinical referral.

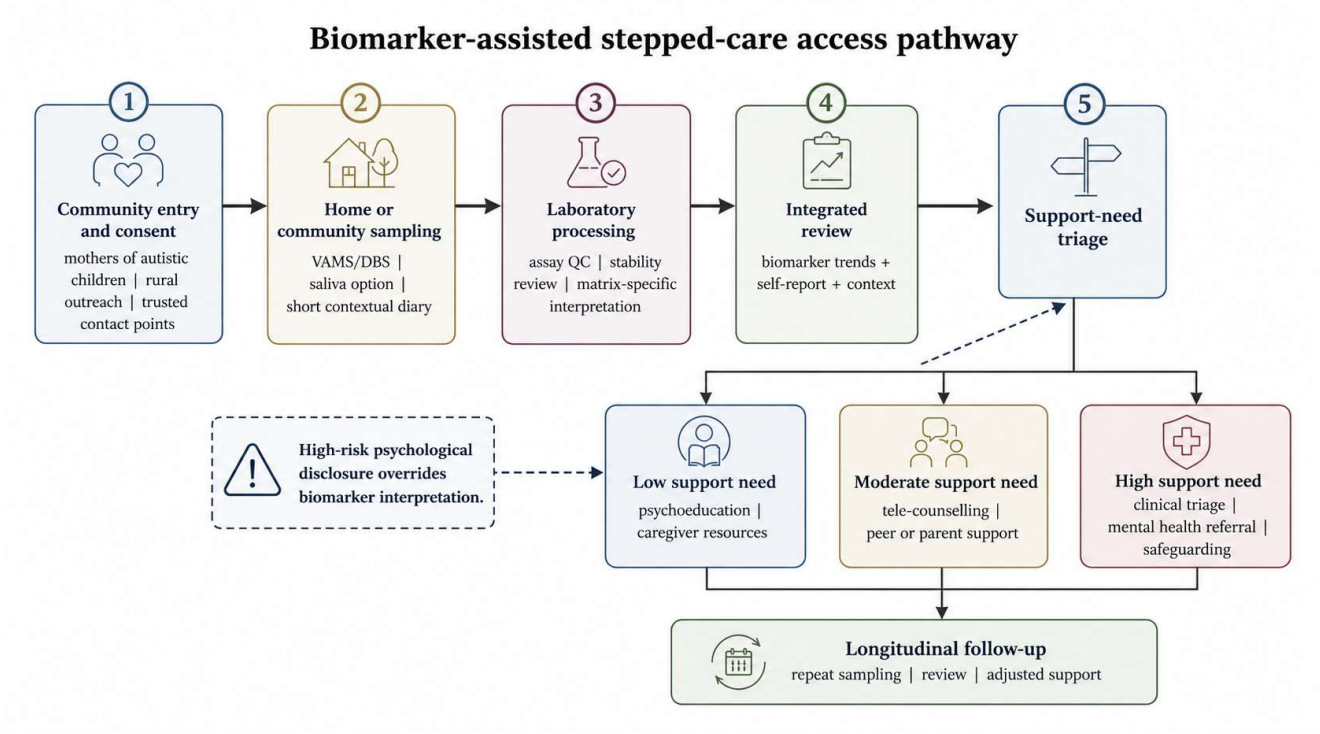

Figure 5. Biomarker-assisted stepped-care access pathway.

Note. The model links biomarker trends, psychological scales and diaries to practical support routes. It draws on telehealth parent-training, rural telemental health, CHW mental health models and LMIC caregiver-support evidence (Adedipe & Walton, 2025; Butzner & Cuffee, 2021; Daniel & Maulik, 2023; Gustafson & Torres, 2024; He et al., 2024; Pacione, 2022; Watanabe et al., 2023).

7.1 Role allocation

A common weakness in framework papers is vague implementation responsibility. A rural microsampling pathway requires explicit role allocation. Laboratories should validate assays, conduct quality control and report results using plain-language interpretive categories. CHWs or family navigators can explain kits, support completion, protect privacy choices and assist referral navigation. Mental health clinicians should lead risk assessment and clinical triage. Autism service providers should connect maternal support with child-focused training. Primary care teams should interpret physical health and inflammatory findings. Researchers should monitor fidelity, cost, sample quality and equity drift.

Table 7 specifies how these actors interact. The table is deliberately practical because rural systems often fail not through lack of intention but through unclear handoffs.

Table 7. Role allocation in a biomarker-assisted rural access pathway

Actor	Core responsibility	Boundary condition	Quality indicator
Laboratory team	Assay validation, sample receipt, QC, matrix-specific interpretation and report generation.	Should not assign mental health diagnoses from biomarkers.	Rejection rate, QC pass rate, turnaround time, matrix agreement reporting.
CHW or family navigator	Kit explanation, diary support, privacy check, referral navigation and follow-up reminders.	Should not interpret biomarkers beyond scripted feedback.	Completion support, participant satisfaction, referral follow-through.
Mental health	Clinical triage, counselling, safety	Should integrate biomarker	Referral uptake, symptom

Actor	Core responsibility	Boundary condition	Quality indicator
clinician	planning and referral decisions.	data with clinical assessment, not replace it.	change, crisis-response adequacy.
Autism service provider	Parent training, child-behaviour support and service navigation.	Should not frame maternal stress as parental failure.	Caregiver skill confidence, child-related stress reduction.
Primary care provider	Review physical health, medication, endocrine or inflammatory confounders.	Should not over-medicalise psychosocial stress.	Follow-up for abnormal physical health indicators.
Research or evaluation team	Data governance, implementation fidelity, cost analysis and equity audit.	Should avoid extracting data without improving support pathways.	Reach, retention, equity metrics and adverse feedback monitoring.

Note. The role allocation reflects task-sharing, rural access and CHW integration principles from telehealth, community health and autism caregiver intervention literature (Adedipe & Walton, 2025; Daniel & Maulik, 2023; Gustafson & Torres, 2024; Kaseje et al., 2024; Pacione, 2022; Shrestha et al., 2024).

7.2 Feedback and referral protocol

Result feedback should be framed as supportive risk formulation. A low-support result might lead to psychoeducation, peer support and repeat monitoring. A moderate-support result might lead to tele-counselling, CHW check-in and autism-specific caregiver training. A high-support result should trigger clinical triage, especially when psychological scales indicate severe distress, self-harm risk, domestic violence or inability to maintain caregiving routines. Any high-risk psychological score or disclosure of self-harm should override biomarker interpretation and trigger immediate referral according to local safeguarding protocols.

Feedback should avoid language such as “abnormal stress biology.” Better wording is: “Your recent pattern suggests a higher stress load than your previous sample, and your questionnaire score also shows strain. We recommend a follow-up conversation to decide what support would be useful.” This language preserves agency and reduces blame. It also avoids overstating the precision of biomarker interpretation, a concern highlighted in work on returning biomarker results to research participants (Robillard et al., 2024).

Caregiver training should also be designed as a relevant, practice-based component of the support package. Rural parent capacity-building and virtual stress-management studies suggest that accessible training can reduce strain when it is practical, context-aware and sustained (Abdat et al., 2023; He et al., 2024; Pacione, 2022; Proctor et al., 2024). Programme design should therefore treat maternal motivation, learner autonomy and learning commitment as conditions for uptake. Although Zhang (2026) examines sustainability-oriented teaching rather than autism caregiving, the study is useful here only at the level of programme design: perceived relevance, motivational internalisation and commitment help explain why support is more likely to be sustained when participants can see its connection to everyday responsibilities. In the present framework, this means that mothers are more likely to remain engaged when follow-up support is visibly relevant to caregiving and livelihood constraints.

8. Ethics, Equity and Governance

Ethical design is not an appendix to this topic; it is central to whether microsampling improves access. The main risks are maternal blame, unsupported disclosure, privacy breach, unequal participation and future misuse of samples or data. Table 8 summarises safeguards that should be built into study design before recruitment.

Table 8. Ethical and equity safeguards for rural microsampling studies

Risk	Why it matters	Required safeguard	Evaluation question
Maternal blame	Stress signals may be misread as poor coping or deficient parenting.	Frame elevated stress as unmet support need; train staff in non-judgemental feedback.	Do mothers report feeling supported rather than blamed?
Unsupported disclosure	Biomarker feedback may increase anxiety if no help is available.	Return results only with clear explanation and referral options.	Does feedback lead to practical support within a defined timeframe?
Small-community privacy	Rural mothers may fear being seen seeking mental health help.	Offer preferred contact modes, discrete packaging and private telehealth options.	Do participants feel their privacy was protected?
Digital exclusion	Telehealth can exclude mothers without broadband, devices or private space.	Provide phone, CHW-assisted or in-person alternatives.	Are low-digital-access mothers retained and referred at similar rates?
Sample and data reuse	Future use may exceed original consent expectations.	Specify retention period, storage, destruction, secondary use, withdrawal procedures and explicit opt-in consent for future use.	Can participants understand and control future sample use?
Equity drift	Programmes may reach easier-to-contact mothers and miss the most burdened.	Track reach by income, distance, language, digital access and caregiving intensity.	Does the programme reduce or widen rural access gaps?

Note. The safeguards combine rural privacy concerns, return-of-results ethics and CHW/telehealth implementation principles (Gustafson & Torres, 2024; Kaseje et al., 2024; Robillard et al., 2024; Watanabe et al., 2023).

Consent should be specific. Mothers should know which samples are collected, which biomarkers are measured, whether samples are destroyed after analysis or stored for re-analysis, who can access results, whether data may be used in future studies and how withdrawal works. The retention period for biospecimens and derived biomarker data should be specified before recruitment. Future use of samples should require explicit opt-in consent rather than broad implied permission. Mothers should also be allowed to decline individual biomarker feedback while still receiving psychosocial resources.

Result return requires responsibility. Biomarker findings are often probabilistic, context-sensitive and difficult to explain. Robillard et al. (2024) identify complexity, precision and responsibility as central considerations in biomarker result return. In this framework, responsibility means that the research team must not disclose stress-related findings without a pathway for explanation, support and escalation. The mother should not be left to interpret a laboratory value alone.

Privacy is especially important in small rural communities. A CHW visit, a telehealth appointment or a package from a health programme may reveal sensitive information. Participants should choose contact modes, appointment times and whether they prefer home, school, clinic or neutral community collection. Data governance should also account for local relationships; the person helping with collection may be known to the family.

Equity evaluation should be active rather than assumed. Programmes that require smartphone use, repeated online diaries or fast mail return may preferentially include mothers with more resources. The development framework therefore treats sample rejection, missed visits and incomplete diaries as equity data. If the most burdened mothers are least

able to complete the protocol, the protocol needs redesign.

9. Research Propositions and Future Study Designs

The field is not yet ready for universal clinical thresholds. It is ready for carefully designed empirical studies. The following propositions are not intended as confirmatory hypotheses for a single study. They define a staged research agenda moving from feasibility to longitudinal modelling and implementation testing.

Proposition 1: Mothers of children with autism in rural agricultural communities will show heterogeneous stress trajectories rather than a single high-stress profile. These trajectories are likely to vary with child sleep and behaviour, service access, maternal sleep, family support, farm workload and financial strain.

Proposition 2: Biomarker trajectories will add greater interpretive value when modelled with sleep disruption, caregiving-event diaries and agricultural workload than when analysed as isolated analyte concentrations.

Proposition 3: DBS or VAMS collection will improve participation among mothers facing travel and clinic-access barriers only when protocols are short, culturally acceptable, supported by CHWs or navigators and designed for imperfect home environments.

Proposition 4: Biomarker-assisted stepped care will improve referral uptake only when feedback is delivered through trusted channels and accompanied by immediate, affordable support options.

Proposition 5: Agricultural exposures, seasonal workload, heat, illness, medication, lactation and sleep disruption will moderate biomarker interpretation and should be measured as core covariates.

Proposition 6: The equity value of microsampling will depend less on assay novelty than on whether the pathway reaches mothers who are usually excluded from clinic-based mental health services.

Future studies can operationalise these propositions in three designs. A feasibility study can compare self-collected VAMS/DBS, saliva and hair in a small rural caregiver sample. A longitudinal cohort can model stress trajectories across school and agricultural seasons. A hybrid effectiveness-implementation trial can test whether biomarker-assisted feedback increases referral uptake, counselling engagement and perceived support compared with enhanced usual care. Across all designs, adverse feedback effects and privacy concerns should be measured explicitly.

10. Discussion

10.1 Theoretical implications

The central implication of this review is that microsampling can improve rural maternal mental health access only when analytical validity, contextual interpretation and care consequences are designed together. In autism caregiver research, biomarkers are often peripheral. In rural health access research, physiology is rarely foregrounded. This review joins these conversations while resisting the claim that biomarkers can solve rural maternal distress by themselves.

This argument extends caregiver stress theory by making service ecology part of the stress pathway. A mother's physiological stress pattern may reflect not only individual resilience or child behaviour but also delayed diagnosis, transport cost, lack of respite, seasonal labour and the absence of autism-informed local support. The implication is that biomarker interpretation should be ecological rather than individualising.

10.2 Methodological implications

Methodologically, the review calls for designs that are smaller, slower and more precise at the beginning. A large sample with weak validation and poor contextual data is less useful than a smaller study that accurately documents matrix performance, sampling burden, missingness and referral consequence. Future studies should publish sample rejection rates, drying and transport conditions, diary completion, time-of-day adherence and reasons for missing samples. These details determine whether the method can travel from laboratory to rural household.

The review also cautions against relying on correlations when comparing microsampling and reference matrices. Agreement, bias and limits across concentration ranges are more important for interpretation. This point is well aligned with recent discussions of bridging microsamples and conventional matrices in metabolic biomarker analysis (Thaitumu et al., 2025).

10.3 Practice and policy implications

For rural health systems, microsampling may become useful when it is combined with tele-mental health, CHW navigation and autism-specific caregiver support. Telehealth can reduce travel burden, but it does not remove digital exclusion or privacy concerns (Butzner & Cuffee, 2021; Watanabe et al., 2023). CHWs can help bridge trust and navigation, yet their role requires training, supervision and clear boundaries (Daniel & Maulik, 2023; Gustafson & Torres, 2024; Kaseje et al., 2024; Shrestha et al., 2024).

For autism services, the framework suggests that maternal mental health should not be treated as separate from child support. Interventions that reduce child behavioural stressors, improve parent confidence and support family routines may also reduce maternal strain. Telehealth parent-training studies in developmental disability contexts support this direction, but engagement and equity require careful monitoring (Adedipe & Walton, 2025; Pacione, 2022; Yesilkaya & Magallon-Neri, 2024).

For laboratories, patient-centred sampling requires field-centred validation. Ambient transport, humidity, delayed return, underfilled devices and missing diaries are not peripheral operational problems. They shape the validity of the result. Laboratory reports should therefore include sample-quality flags and interpretation limits, not only numeric values.

10.4 Limitations

This review has limitations. It is a critical integrative review rather than a systematic review or meta-analysis. Its purpose is to develop a translational framework, not to estimate pooled associations between biomarkers and maternal distress. The direct evidence base on microsampling among mothers of children with autism in rural agricultural communities remains limited. As a result, some recommendations are extrapolated from adjacent fields, including DBS inflammatory research, VAMS steroid analysis, rural telehealth, CHW models and autism caregiver intervention studies.

The proposed framework also requires adaptation by country, health system and cultural context. Rural agricultural communities differ in land ownership, migrant labour, gender norms, primary care coverage, autism service infrastructure and laboratory capacity. A model feasible in one setting may not transfer directly to another. This is why the first phase is community co-design rather than immediate deployment.

11. Conclusion

Mothers of children with autism in rural agricultural communities often carry stress that is continuous, embodied and difficult to make visible within conventional service systems.

Microsampling-enabled stress biomarker bioanalysis offers one possible route to earlier recognition, but only if it is developed with analytical discipline and ethical restraint. Its value lies not in diagnosing maternal mental health from a biological sample, but in opening a structured route for follow-up when chronic stress burden would otherwise remain hidden.

A responsible programme must combine validated microsampling methods, conservative biomarker interpretation, maternal self-report, contextual diaries, CHW or navigator support, tele-mental health, autism-specific caregiver resources and culturally safe referral pathways. Used carefully, microsampling may help convert otherwise hidden stress burden into a structured opportunity for follow-up, provided that biomarker interpretation is linked to accessible, non-stigmatising and culturally safe care. Used poorly, it would add another layer of measurement to lives already shaped by surveillance, stigma and service scarcity. The development task is therefore not simply to miniaturise sampling, but to build a pathway in which every biological signal has a credible route to conversation, support and protection.

Declarations

Ethics approval and consent to participate: Not applicable. This article is a critical review and development framework and does not report primary human participant data.

Consent for publication: Not applicable.

Availability of data and materials: No new datasets were generated or analysed for this article.

Competing interests: The authors declare no competing interests.

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Authors' contributions: Yan Yan conceptualised the article, developed the review structure and drafted the manuscript. Erlina Binti Abdullah supervised the conceptual development, reviewed the framework and revised the manuscript for intellectual content. Both authors approved the final manuscript.

Supplementary Appendix A. Search terms and evidence mapping

The review used four search clusters: (1) autism/autistic children/autism spectrum disorder; (2) maternal mental health/caregiver stress/parenting stress/caregiver burden; (3) rural health/agricultural communities/farmer mental health/farmworker mental health; and (4) microsampling/dried blood spot/volumetric absorptive microsampling/saliva cortisol/hair cortisol/bioanalytical validation. Evidence was mapped to four domains: caregiver stress, rural access, biomarker interpretation and microsampling implementation. The appendix is provided to clarify the critical-review logic and should not be read as a PRISMA extraction record. Evidence was prioritised for its contribution to framework development and responsible implementation rather than for pooled effect estimation.

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