Original research

Randomised controlled trial for the titration of oral corticosteroids using markers of inflammation in severe asthma

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ABSTRACT

Introduction Biomarkers are used to select biologic therapies for patients with severe asthma, but not to regularly adjust therapy, especially oral corticosteroids (OCS).

Objective Our goal was to test the efficacy of an algorithm to guide the titration of OCS using blood eosinophil count and fraction of exhaled nitric oxide (FeNO) levels.

Design, participants, interventions and setting This proof-of-concept prospective randomised controlled trial assigned adult participants with severe uncontrolled asthma (n=32) to biomarker-based management (BBM) where OCS dose was adjusted based on a composite biomarker score comprised of blood eosinophil count and FeNO, or a standard best practice (SBP) arm. The study was conducted at the Hunter Medical Research Institute, Newcastle, Australia. Participants were recruited from the local Severe Asthma Clinic and were blinded to their study allocation.

Main outcome The coprimary outcomes were number of severe exacerbations and time to first severe exacerbation assessed over 12 months.

Results There was a longer median time to first severe exacerbation with BBM, although not significant (295 vs 123 days, Adj. HR: 0.714; 95% CI: 0.25 to 2.06; p=0.533). The relative risk of a severe exacerbation in BBM (n=17) vs SBP (n=15) was 0.88 (Adj.; 95% CI: 0.25 to 2.06; p=0.533). The relative risk of a severe exacerbation in BBM (n=17) vs SBP (n=15) was 0.88 (Adj.; 95% CI: 0.47 to 1.62; p=0.675) with a mean exacerbation rate per year of 1.2 and 2.0, respectively. There was a significant reduction in the proportion of patients requiring an emergency department (ED) visit using BBM (OR 0.09, 95% CI: 0.01 to 0.91; p=0.041). There was no difference in the cumulative OCS dose used between the two groups.

Conclusion A treatment algorithm to adjust OCS using blood eosinophil count and FeNO is feasible in a clinical setting and resulted in a reduced odds of an ED visit. This warrants further study to optimise the use of OCS in the future.

Trial registration number This trial was registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12616001015437).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There have been multiple studies employing novel therapies and biomarker-based management (BBM) to improve outcomes in patients with severe asthma, with studies employing biologic medications demonstrating a significant reduction in the use of chronic systemic corticosteroid. Despite this, there remains a significant proportion of the population who continue to require treatment with oral corticosteroids (OCS) for various reasons and very little randomised controlled data to help guide management for these patients in an objective fashion using readily available biomarkers.

WHAT THIS STUDY ADDS

⇒ We sought to determine whether controlling airway inflammation by titrating OCS using a biomarker composite score made up of PBE and fraction of exhaled nitric oxide as a surrogate for spum induction determined airway eosinophilia will reduce exacerbations in patients with severe asthma, compared with usual care alone, in a severe asthma clinic. This BBM approach proved feasible, although the primary endpoint of a reduction in severe exacerbation rate was not met, but a reduction in the proportion of patients who required an emergency department visit was observed, without a significant difference in the cumulative amount of OCS used.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This furthers the concepts of precision medicine for the chronic management of severe asthma using objective biomarkers to improve outcomes for patients, reduce healthcare resource utilisation, and serve as a catalyst for future work in this field.

INTRODUCTION

Asthma affects approximately 340 million people worldwide, with an ever increasing prevalence, particularly in developed nations. Recent estimates suggest approximately 4% of this population have severe refractory disease.2 This population, although small, disproportionately accounts for up to half the healthcare resource use and direct and indirect costs to society due to asthma.1 Thus, optimisation of the management of asthma in this population represents an important opportunity for the improvement of asthma care. While there has been
significant progress in the last 75 years in the availability of treatments for the asthma population, in general, it would appear that improvements in morbidity and mortality have plateaued over the last decade, with only small incremental gains. Biologic agents have been a significant advancement for the management of severe asthma for those patients with refractory type 2 airway inflammation demonstrating benefit in reducing the use of oral corticosteroids (OCS) for episodic exacerbations and, in the case of mepolizumab, benralizumab, and dupilumab, reducing their use for regular maintenance treatment as well. Optimisation of the use of OCS in this population is important to ensure that risk is reduced and benefit maximised. Preclinical work has demonstrated the utility of titrating therapy based on sputum eosinophil counts and fraction of exhaled nitric oxide (FeNO). Unfortunately, sputum cell count measures remain difficult to obtain at many centres. Peripheral blood eosinophil (PBE) counts, however, are widely available and have been used as a surrogate for sputum cell counts. As a result, we sought to determine whether controlling airway inflammation by titrating OCS using biomarker-based management (BBM) via a composite score made up of PBE and FeNO, as a surrogate for sputum induction determined airway eosinophilia, will reduce exacerbations in patients with severe asthma, compared with standard best practice (SBP) alone, in a severe asthma clinic. Our hypothesis was that this would be feasible and effective for these outcomes, while resulting in a lower cumulative dose of OCS used.

**METHODS**
To explore this, we conducted a prospective randomised, single-blind, controlled proof-of-concept study comparing BBM with SBM based best practice clinical management (SBP) in participants with severe asthma. Potential participants were recruited from the Severe Asthma Clinic at the John Hunter Hospital, New Lambton, New South Wales, Australia. This is a tertiary referral specialist/multidisciplinary severe asthma clinic. All patients of the clinic had been assessed by the clinical team within a structured programme that confirms the diagnosis of asthma, assesses and controls factors that precipitate and trigger asthma, and assesses and treats the presence of comorbid conditions such as upper airway dysfunction, gastroesophageal reflux, rhinitis and obstructive sleep apnoea.

Participants were recruited into the study if they were over 18 years of age, never or ex-smokers, and diagnosed with severe asthma. To be classified as severe, participants had to have been on Global Initiative for Asthma (GINA) Step 4/5 therapy and have had uncontrolled asthma despite this treatment, with either: a 6-point Asthma Control Questionnaire (ACQ) Score ≥ 1.5, or a hospital admission for asthma in the last 12 months or at least two severe asthma exacerbations in the past 12 months requiring a burst of OCS (of at least 3 days). Mepolizumab was introduced into the severe asthma clinic after the initiation of the study protocol and participants taking any biological therapy available were included in the study, but randomisation was not adjusted for type of biological therapy. Participants did not have to be on OCS at baseline to be enrolled. Participants were excluded based on criteria in the online supplemental appendix.

Following a 4-week run-in period where participants remained on their usual asthma treatment, those who remained stable were randomised to either BBM or SBP in a 1:1 ratio. Block randomisation was performed by an independent research associate using computer-generated randomisation tables with stratification based on the presence or absence of OCS maintenance dosing and blood eosinophil count at screening above or below 0.4×10⁹ cells/L.

At baseline, inflammation was assessed with the following markers: exhaled nitric oxide, induced sputum analysis and peripheral full blood count. Participants were followed for a total 12-month period and assessed for outcomes on a monthly basis as per the study visit schedule (online supplemental table 1), with every second visit in the latter half of the study period being conducted by phone. At the end of each in-person visit, medication changes were made according to study arm allocation. Participants and clinicians were blinded to each participant’s treatment group allocation as well as inflammatory marker results.

**Study groups**
In BBM, participants were assessed by a clinician at each visit and adjustment of OCS dose was performed using the algorithm in figure 1 as per the OCS adjustment table in online supplemental table 2 based on the results of their PBE count and FeNO. PBE count and FeNO were used to assign a participant an average biomarker score, which dictated the titration of their OCS dose.

![Blood eosinophil count](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAAAEAAAABCAQAAAC1HAwCAAAAC0lEQVR42mNk7DwABoQgAGwAAAABJRU5ErkJggg==)

**Figure 1** Algorithm for biomarker-based management of oral corticosteroid dose. BBM, biomarker-based management; FeNO, fraction of exhaled nitric oxide; ICS, inhaled corticosteroid; OCS, oral corticosteroids.
Cut points for FeNO had been decided based on prior identifi-
cation of the upper limit of FeNO at which people with asthma
can undergo corticosteroid withdrawal, as well as that which
is associated with control of eosinophilic inflammation.17 Cut
points for PBE have been determined as those previously asso-
ciated with increased airway eosinophilia in asthma and chronic
obstructive pulmonary disease (COPD).11,18

The participants in SBP had their asthma control assessed
according to standard clinical parameters based on GINA treat-
ment guidelines and treatment step or dose escalation or de-es-
calation.19 This was assessed every 4 months through the study,
based on the recommendations of a consultation with a clinician
(see online supplemental table 1). Standard care treatment deci-
sions were made at these particular visits based on the result
of clinician consultation without knowledge of biomarker results
for that visit. This was based on the standard clinical care prac-
tice in the Severe Asthma Clinic at the John Hunter Hospital.

An additional analysis was performed on the subgroup
of patients receiving mepolizumab, as it was expected their
biomarkers may be affected by this treatment. PBE and FENO
over the course of the study were measured in this cohort.

Outcomes
The coprimary outcomes were time to first and the number
of severe exacerbations over 12 months. An asthma exacerba-
tion was defined as a worsening of asthma control character-
ised by a progressive increase in symptoms requiring a change
in treatment. Severe exacerbations were defined as those
requiring systemic glucocorticoids or an increase in the dose of
regular systemic glucocorticoids for at least 3 days.20 Secondary
outcomes that were assessed were change in asthma symptom
scores using the Asthma Control Questionnaire (ACQ),16 and
Asthma Quality of Life Questionnaire (AQLQ).21 total and
maintenance dose of OCS, analysis of markers of inflammation
at the final visit compared with entry (PBE, sputum eosinophil
counts and FeNO), total dose of OCS used during the period of
the study, and hospital admission or emergency room visit due
to asthma

Spirometry, FeNO and sputum and blood eosinophil
measurements
FeNO measurements were performed using a NIOX VERO
(Aerocrine, Sweden) device, as per the manufacturer’s sugges-
tions and prior to spirometry. Spirometry was performed as per
American Thoracic Society (ATS) criteria21 using a MedGraphics
CPFS/D USB-Ascensia spirometer and BreezeSuite software
(Minneapolis, USA). Blood eosinophil counts were measured
from samples obtained at each in-person visit through the study
and processed at either Pathology North (New South Wales,
Australia) laboratories or the Hunter Medical Research Institute.
Sputum induction and processing were performed as previously
described by Gibson et al.22

Statistical considerations
All analyses were conducted using SAS V9.4. An intention-to-
treat analysis was performed for all randomised participants.
Frequencies and percentages are provided for the categorical
variables, while means, SD, median, first and third quartiles are
provided for the continuous variables.

Time to first severe exacerbations was compared between
treatment arms using a Kaplan-Meier plot, along with a log-rank
test for the crude models and Cox regressions for both the crude
and adjusted models. Negative binomial models were used to
analyse the total number of severe exacerbations between treat-
ment arms.

For the secondary outcomes that were recorded more than
once, treatment arms were compared using linear mixed model-
ing with random intercepts for within-subject correlation over
time. Where the outcome was measured only once, treatments
were compared using linear regression. Due to the low counts
of hospital/emergency department (ED) visits and a small subgroup
sample size for the participants on mepolizumab, the variables
for the former were dichotomised to having had a hospital/ED
visit versus not, logistic regression was used to compare the two
treatment arms, and only crude models were used. Adjusted
models are presented for each other outcome, which have been
adjusted for age, sex, body mass index, education, smoking
history, age at asthma diagnosis, baseline blood eosinophil count
and baseline prednisolone dose.

Sample size was calculated based on uncontrolled prior data23
demonstrating a reduction in exacerbations from a median of
5 (IQR 5–8) to 0 (IQR 0–1) with the use of a similar algorithm
based on PBE for asthma management. Assuming α=0.05, and
allowing power to range from 0.8 to 0.95, yields a desired range
of sample sizes for each of the two groups of 9–16. Thus, a
conservative estimate of the necessary total sample size was 30.

RESULTS
Of the 41 patients screened, 32 were eligible for randomisation;
17 were randomised to BBM and 15 to SBP from 9 January 2017
to 23 May 2018, with 29 completing the study (online supple-
mental figure 1). The study was ended once the required sample
size was reached and the last participant completed all required
visits. A total of 32 patients were analysed in the intention-to-
treat analysis. In BBM, one participant was lost to follow-up
due to poor health and inability to attend study visits, and one
was removed due to an adverse reaction to OCS. In SBP, one
participant discontinued the study to undergo investigation for
a newly discovered potential malignancy. Baseline measurements
for participants are presented in table 1.

There were less ex-smokers in BBM versus SBP (29% vs 47%);
however, the mean pack-year history was higher in BBM (17.9 vs
7.2 pack-years), both variations likely due to a small sample size.
Mean baseline lung function was similar between the groups, as
was mean sputum eosinophil count percentage (5.2% in BBM
vs 6.0% in SBP) and exacerbation frequency in the last year (3.9
exacerbations/year vs 4.8) (table 1). With respect to the markers
of inflammation that would form the basis for the composite
biomarker score and adjustment of corticosteroid dose during
the study, blood eosinophils were similar while FeNO was lower
in BBM (24) vs SBP (43). The median baseline dose of oral predn-
isolone was the same between the groups at 5 mg/day.

Outcomes
Median time to first severe exacerbation was more than two
times as long at 295 days with BBM vs 123 days with SBP, though
this was not statistically different (Adj. HR: 0.71; 95% CI: 0.25
to 2.06, p=0.333) (table 2, figure 2). There was no significant
difference in the number of severe exacerbations with BBM
versus SBP (table 2, figure 2).

There was a significant difference in the proportion of partic-
ipants who had at least one ED visit with a reduced OR with
BBM versus SBP (OR: 0.09 95% CI: 0.01 to 0.91, p=0.041)
table 2). Similarly, the proportion of patients with at least one
hospitalisation for asthma appeared to be reduced with BBM
but this was not statistically significant (OR 0.37 95% CI 0.06
This was done correctly (47/51 times in BBM (92.2%, 95% CI: 84.8% to 99.5%) vs 11/12 times in SBP (91.7%, 95% CI: 76.0% to 107.3%), p=0.955).

A subgroup analysis of PBE and FeNO levels for those participants on mepolizumab also did not demonstrate any significant difference over time, regardless of treatment arm (online supplemental figure 3). This may be related to the suppressive effect of this medication on eosinophils. In spite of this, in 18.2% (95% CI: 8.9% to 27.5%) of all visits among participants on a biologic in BBM vs 40.0% (95% CI: 29.9% to 50.1%, p=0.004) in SBP biomarker measures were detectable and still elevated (FeNO>30 ppb or PBE>0.3 x 10³ cells/L).

Unfortunately, this study was underpowered to detect its primary outcomes due to an insufficient sample size. Post-hoc analysis revealed that 286 subjects would have been needed to provide a power of 80% to detect a difference at α=0.05 for the HR and time to events observed in the study.

**DISCUSSION**

Our results demonstrate that a biomarker-based approach to the management of OCS in patients with severe asthma is feasible within a tertiary care severe asthma clinic. However, we were unable to demonstrate a significant difference in the coprimary outcomes of number of severe exacerbations and time to first exacerbation. While not significant, median time to first severe exacerbation in BBM was 295 days compared with only 123 days in SBP. The biomarker strategy may have had a greater impact on reducing more severe exacerbations as fewer participants in this arm experienced an exacerbation requiring an ED visit compared with the standard care arm and there was a trend towards a reduced proportion of participants requiring hospitalisation. Cumulatively, there was no statistical difference in the total dose of OCS used in the two treatment arms to achieve these outcomes. Unadjusted OCS trends over time were similar in both groups (online supplemental figure 4).

A reduction in ED visits is important since a large proportion of the costs attributable to the care of patients with severe asthma is associated with healthcare utilisation. In addition, recurrent emergency visits and hospitalisations are key components of severe asthma that affect quality of life for these patients. The ability to influence the need for healthcare utilisation without increasing the cumulative dose of OCS administered would be beneficial to this patient group. However, this reduction in ED costs would need to be offset against the increased number of visits required to achieve the adjustment of inflammation as participants in the biomarker arm attended monthly visits compared with 16-weekly visits in the standard care arm.

Interestingly, similar research conducted by Heaney et al has sought to use a composite biomarker-based approach incorporating FeNO, PBE and periostin. Participants in this study had their therapy adjusted based on their biomarkers every 8 weeks over a 48-week period, compared with usual care. Although failing their primary endpoint in the intention-to-treat analysis, a significant proportion of patients were able to reduce their corticosteroid dose in the per-protocol analysis. There was a similar, but not significant, trend towards reduced exacerbation rates. This difference in ability to reduce corticosteroids, but ultimate inefficacy, may be related to the different biomarkers used, for example, periostin was included in the work by Heaney et al compared with this study. Alternatively, the cut-offs chosen in the algorithm studied here may have limited the opportunity for reduction of corticosteroid, and conversely may have been too stringent with respect to reducing dose changes. In addition,

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**Table 1** Baseline demographics of participants in standard best practice (SBP) and biomarker-based management (BBM) arms

<table>
<thead>
<tr>
<th>Demographic</th>
<th>BBM, n=17</th>
<th>SBP, n=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>60.2 (13.6)</td>
<td>61.2 (10.5)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>35%</td>
<td>47%</td>
</tr>
<tr>
<td>Highest level of education</td>
<td>&lt;Year 11 5 (36%)</td>
<td>8 (50%)</td>
</tr>
<tr>
<td></td>
<td>Year 12 3 (21%)</td>
<td>1 (6.3%)</td>
</tr>
<tr>
<td></td>
<td>Diploma 1 (7.1%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td></td>
<td>Certificate III/IV 3 (21%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td></td>
<td>Bachelors 2 (14%)</td>
<td>1 (6.3%)</td>
</tr>
<tr>
<td></td>
<td>Graduate/ postgraduate degree 0 (0%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>29%</td>
<td>47%</td>
</tr>
<tr>
<td>Pack-year history</td>
<td>17.9 (16.5)</td>
<td>7.2 (6.0)</td>
</tr>
<tr>
<td>Forced expiratory volume in one second (% predicted)</td>
<td>72.7 (18.9)</td>
<td>67.8 (17.8)</td>
</tr>
<tr>
<td>Peripheral blood eosinophil (cells×10⁹/L)</td>
<td>0.3 (0.3)</td>
<td>0.5 (0.5)</td>
</tr>
<tr>
<td>Fraction of exhaled nitric oxide (ppb)</td>
<td>24.3 (29.1)</td>
<td>42.7 (64.4)</td>
</tr>
<tr>
<td>Prednisolone dosage (mg/day)</td>
<td>4.7 (6.6)</td>
<td>5.4 (7.1)</td>
</tr>
<tr>
<td>Number with daily oral corticosteroids use (%)</td>
<td>9 (52.9%)</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Asthma Control Questionnaire-6 Score</td>
<td>2.2 (1.2)</td>
<td>1.8 (1.3)</td>
</tr>
<tr>
<td>Exacerbations in the last year</td>
<td>3.9 (2.9)</td>
<td>4.8 (3.6)</td>
</tr>
<tr>
<td>Sputum eosinophil count (%)</td>
<td>5.2 (7.2)</td>
<td>6.0 (8.7)</td>
</tr>
<tr>
<td>Presence of eosinophilic airway inflammation</td>
<td>7 (41.2)</td>
<td>8 (53.3)</td>
</tr>
<tr>
<td>Biologic treatment for asthma (n, %)</td>
<td>6 (35%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>2 (11.8%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>4 (23.5%)</td>
<td>8 (53.3%)</td>
</tr>
<tr>
<td>Key comorbidities, (n, %)</td>
<td>12 (71%)</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>Gastroesophageal reflex disease (GORD)</td>
<td>16 (94%)</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Sinonasal disease</td>
<td>9 (52%)</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>8 (47%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>1 (6%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Vocal cord dysfunction</td>
<td>3 (18%)</td>
<td>5 (33%)</td>
</tr>
</tbody>
</table>
| Allergic bronchopulmonary aspergillosis (ABPA)/fungal disease | Data presented as number (proportion (%)) or mean (SD).

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while a lack of participants choosing to follow the treatment directives given at visits in the Heaney et al work was thought to affect the ability to demonstrate an effect, this is not thought to be the case in this study cohort, as adherence was high, as monitored through the study based on pill counts, and treatment decisions were followed the vast majority of the time in both groups. The authors postulate that, while titration of asthma therapy according to sputum eosinophilia has been successful in prior studies, peripheral blood eosinophilia and FeNO may not be direct enough measures of type 2 high inflammation or not sufficiently correlated with exacerbation risk, to be as useful for the adjustment of therapy longitudinally. Novel biomarkers may need to be considered in the future. Similarly, this strategy may not apply to patients without eosinophilic airway inflammation, and these participants comprised 53% of our population (table 1). Interestingly, in the studied population, among those participants on a biologic treatment, either FeNO or PBE remained detectable in upwards of 40% of participant visits, suggesting the composite biomarker score could still be considered a useful measure on which to base adjustments of medications in the biologic era (online supplemental figure 3). Direct conclusions on whether this weakened the effect of our intervention cannot be determined, however, due to the small numbers analysed. This likely affected the results with respect to time to first severe exacerbation (figure 2).

Further advances in artificial intelligence and machine learning may better allow for widespread utilisation of biomarkers as a guide, in this setting. Machine learning could allow for the exploration of which biomarkers, and at which levels, ideally predict good asthma control and improved outcomes, similar to what is being considered in other fields such as cardiology and oncology for their outcomes.

### Benefits of the study and limitations

This study benefitted from its randomised and blinded design. Although participants were assessed equally as many times in both arms of the study, decisions were only made in SBP every 4 months, thus there were fewer opportunities to change the course of asthma control. Conversely, the small sample size may have limited the ability to identify a true effect. Unfortunately, although this was a pilot study with a sample size based on prior observed effects, it appears to have been underpowered to detect the primary outcome based on post-hoc calculations. A larger multicentre trial would allow for larger numbers as well as greater generalisability of the results. In addition, being a single-centre study based at a clinic specialised in the treatment of patients with severe asthma, the participants treated as per the clinical judgement of the study physicians would likely already reflect optimisation of the role of steroids in ongoing treatment.
Figure 3  Asthma Control Questionnaire-6 Score (ACQ6) (A) and Asthma Quality of Life Questionnaire (AQLQ) (B) mean scores over time in the biomarker-based management (BBM) and standard best practice (SBP) groups.
Clinicians were also not blinded to the fact that participants were enrolled in the study.

Further, the study was impacted by the introduction of mepolizumab as a treatment for severe asthma in our clinic after the study commenced. Due to the timing of availability of mepolizumab in Australia, the authors felt it would be unethical to disallow participants from accessing this novel therapeutic, but allowed for inclusion after 6 weeks of stability. Randomisation was not adjusted for this, and hence, our results may have been impacted by the differential effects of mepolizumab in our study population.

CONCLUSION
A treatment algorithm to adjust OCS using blood eosinophil count and FeNO is feasible in a clinical setting. There was a trend towards a longer time to severe exacerbation and reduced odds of a hospital admission, although these results were not significant. The treatment algorithm did result in a reduced proportion of patients requiring an emergency visit for their asthma, without a significant difference in the cumulative amount of OCS used. This warrants further study in a larger sample to optimise the use of OCS with biomarkers in the future.

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