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Implementation of a preemptive pharmacogenetic passport: Acceptance, attitudes and preferences of the general population

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ABSTRACT

Background: Implementation of pharmacogenetic (PGx) testing remains largely limited to reactive single-gene testing. Preemptive multi-gene testing can more effectively guide drug prescription, but requires public acceptance for successful implementation.
Aims: To evaluate acceptance, attitudes, and preferences regarding a preemptive multi-gene PGx passport among participants from the general population.
Methods: Participants from Lifelines, a Dutch population-based cohort, were offered a personalized PGx passport through a smartphone application and invited to complete baseline and follow-up questionnaires.
Results: Of 4344 invitees, 1178 completed the baseline questionnaire (27.1%), and 995 (84.5% of respondents; 22.9% of invitees) accepted their PGx passport. Reassurance about medication ineffectiveness was the main reason for acceptance (73.6%). Lack of need was the main reason for declining the passport in general (32.0%), while reasons for declining app-based delivery included not wanting an app (47.3%) and privacy concerns (43.2%). Attitudes were highly positive, though declined slightly after receiving the passport ($p = .007$), with main concerns being privacy and data safety. Participants preferred preemptive testing (57.9%), although attitudes were slightly more positive towards single-gene than multi-gene testing ($p = .029$). Moreover, participants prioritized medication users and specialist care patients over all individuals (both $p < .001$), favored exclusive personal access to their results over direct sharing with healthcare professionals ($p < .001$), and preferred digital delivery formats (69.4%).
Conclusions: Respondents were generally open to preemptive PGx testing, favoring digital delivery and personal control over result access. Implementation should address privacy concerns and consider prioritizing medication users and patients receiving specialist care.

1. Introduction

Pharmacogenetic (PGx) testing examines how genetic factors affect a patient's response to medication, enabling personalized drug prescription when a drug-gene interaction is identified.[1,2] Implementation of PGx testing is still largely restricted to reactive single-gene testing, which is performed after patients experience (severe) adverse drug reactions (ADRs) or when the medication proves ineffective.[3] Preventive PGx testing is done before treatment initiation and includes both pre-therapeutic and preemptive testing. Pre-therapeutic single-gene testing is conducted when a drug with known drug-gene interactions is prescribed, whereas preemptive multi-gene testing is conducted before and irrespective of any medication use, allowing results to inform future prescribing decisions.[4,5] Although testing costs remain an important consideration, advances in genome-wide testing have made preemptive multi-gene PGx testing increasingly feasible, expanding its potential for population-wide implementation.

Preemptive multi-gene PGx testing offers several advantages for patient care and healthcare efficiency. Firstly, it facilitates faster medication selection and dosing since results are immediately available at the

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point of prescription.[6] Secondly, clinical evidence indicates that genotype-guided prescribing can reduce the risk of clinically relevant ADRs by approximately 30%.[6,7] Finally, it has the potential to reduce healthcare costs by minimizing resources spent on the current trial-and-error approach, as well as those associated with ADRs and ineffective treatments.[6,8] Implementation of preemptive multi-gene PGx testing could have a substantial impact at population level. Approximately 50% of European adults report using prescribed medication.[9] Irrespective of medication use, recent studies indicate that up to 99.7% of individuals carry at least one actionable drug–gene interaction.[10,11] Given the broad potential relevance of PGx testing over time, it is essential to investigate how the general population perceives PGx testing.

However, most research on perspectives regarding PGx testing, particularly acceptance and attitudes, has focused on clinical patient populations and hypothetical scenarios. Overall, patients report positive views, often citing benefits such as improved medication selection and dosing.[12–16] For example, 97–99% of Canadian patients with cancer wanted PGx testing in the presented clinical scenarios, and patients also expressed willingness to pay out of pocket for testing.[13] Among patients in Dutch outpatient hospital care, 92% considered their PGx results useful and 89% comforting.[15] Nonetheless, negative attitudes are also observed, including nervousness or anxiety about results and privacy concerns.[12,16–19] Studies among the general population in the United States have similarly shown high interest in PGx testing, even among those initially unfamiliar with the concept.[20,21] More recently, a nationally representative UK survey found that 89% of respondents would be willing to undergo PGx testing.[22] However, an international survey of 98 patients, predominantly from North America, found that 51% selected “neutral/unaware” when asked about their overall feelings towards PGx testing.[23]

Besides attitudes towards PGx testing, preferences regarding test type and timing, result access, and delivery are relevant to implementation. Previous research in US primary care found that patients valued preemptive PGx testing for its potential to inform future treatment and avoid delays, although some had difficulty understanding this approach.[24] Regarding result access, a US population survey found that 78% of respondents would be unlikely to undergo PGx testing if their results could be shared without their permission.[20] Preferences for receiving PGx results vary across studies. In a small US biobank interview study using hypothetical PGx reports, participants expressed preferences for mailed paper reports, patient portal access, or both.[25] Following PGx testing in US primary care, patients valued a wallet-sized results card for its portability and ease of sharing with clinicians.[24] In a UK population survey, 78% supported making PGx results available in an app, although this did not establish a preference over other delivery formats.[22]

To build on these findings, we conducted a study of a preemptive multi-gene PGx test in a Dutch population cohort, regardless of participants' current medications, clinical needs, or prior PGx knowledge. Participants could receive their personal PGx passport, generated from existing genotype data, through a mobile app. We examined (1) PGx passport acceptance and reasons for accepting or declining, (2) attitudes before and after receiving their PGx passport, and (3) preferences regarding the PGx passport and PGx testing, including target groups (who), test types and timing (what), result access (where), and result delivery format (how).

2. Methods

2.1. Design and sample

This prospective quantitative study investigated acceptance, attitudes, and preferences regarding the personal PGx passport offered to participants and PGx testing in general. This research was conducted in collaboration with the Lifelines Cohort Study, a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 167,729 persons living in the North of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics.[26]

We used a non-probability sampling strategy to select eligible participants from the University Medical Center Groningen (UMCG) Genetics Lifelines Initiative (UGLI), a genotyped Lifelines subcohort comprising 38,030 individuals.[27] This approach allowed us to use existing genetic data while restricting eligibility to individuals whose data met the quality requirements for returning personalized PGx results. These data had previously been used to develop and validate the PGx passport pipeline.[28] Participants had consented to genotyping for general research purposes, not specifically PGx testing.

The participant selection process is shown in Fig. 1. Of the 38,030 individuals, 36,373 passed standard quality control, including checks of data quality, sex concordance, and family relationships. Since quality control procedures in research settings are generally less stringent than those used in clinical diagnostics, additional verification of sample identity was performed using Idéfix, which assesses concordance between recorded phenotypes and phenotypes predicted from genetic data.[29] A strict threshold was applied to minimize the risk of returning results to the wrong individual, resulting in a subset of 5765 individuals. After excluding participants who had withdrawn or died, 4344 active Lifelines participants remained. Eligibility additionally required participants to be aged 18 years or older.

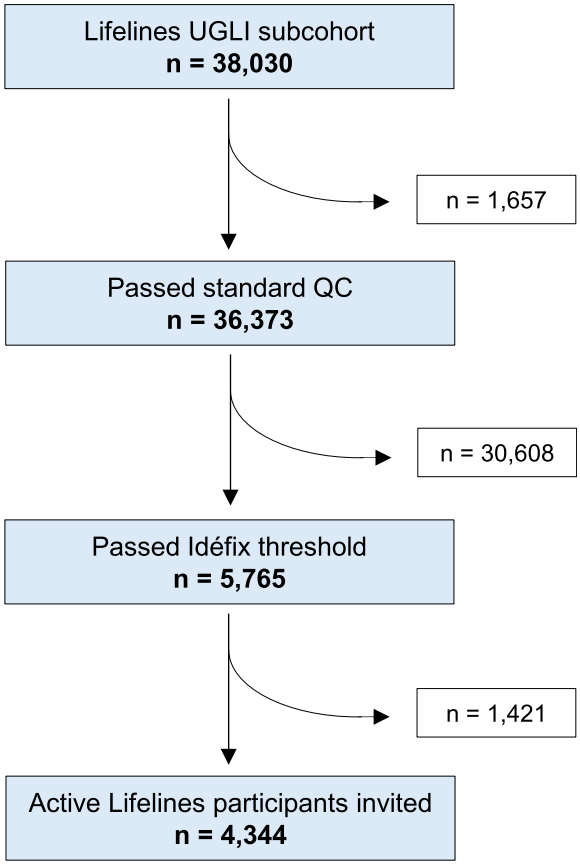

Fig. 1. Flow diagram of participant selection from the Lifelines UGLI subcohort. Side branches indicate exclusions at each step. UGLI, UMCG Genetics Lifelines Initiative, UMCG, University Medical Center Groningen, QC, quality control.

2.2. Procedure

An overview of the current study procedure is shown in Fig. 2. Data collection took place from April to July 2024, with recruitment starting once preparations for the study were complete. Lifelines invited all eligible participants by email to complete the baseline questionnaire (T0), which was open for two weeks. Completion of T0 was required before participants could be invited to provide separate e-consent to receive their personalized PGx passport through a smartphone application. Approximately four weeks after T0 closed, participants who had provided this additional consent received an email invitation from the app developer to download and use the app. Approximately three weeks later, Lifelines invited all participants who had consented to receive their passport to complete the follow-up questionnaire (T1), regardless of whether they had downloaded or used the app.

The study was approved by the Medical Ethics Review Committee of the UMCG (number 2024/177). Informed consent for participation in the Lifelines cohort had been obtained from all participants.

2.3. Measures and materials

2.3.1. Pharmacogenetic passport

PGx profiles were produced with the automated PGx passport pipeline at the UMCG Department of Genetics using the Infinium Global Screening Array multi-ethnic disease (GSA-MD) v.1.0 array.[28] The personalized PGx passport was delivered through the smartphone application Gen en Geneesmiddel (Gene and Medication), developed by Synappz Digital Healthcare, which was paid for app development and technical support. The company was not involved in the study design or data analysis. In the app, users can access their PGx results, view explanations of drug-gene interactions, browse FAQs, and download a technical report designed for their healthcare professionals (Fig. 3). To ensure accessibility and understandability of the PGx information for participants, the text was made layperson-friendly at Common European Framework of Reference for Languages level B2.[30] The drug-gene interactions were based on the Dutch Pharmacogenetics Working Group (DPWG) guidelines.[31]

2.3.2. Questionnaire development

The questionnaires were developed for the specific context of the PGx passport with input from a multidisciplinary research team with expertise in health psychology, questionnaire development, and pharmacy. They combined self-constructed items with items previously used in a study of PGx implementation in Dutch outpatient care, in which questionnaire development was informed by interviews and focus groups with patients, prescribers, and pharmacists.[15] Attitude items were informed by the Theory of Planned Behavior framework[33]. Common response formats, including Likert scales, were used. An earlier version was piloted in Lifelines NEXT, a subcohort of Lifelines.[32] Following the pilot, the questionnaires were shortened to reduce participant burden. Lifelines NEXT participants were excluded from the present study.

2.3.3. Participant characteristics

Participant characteristics were obtained from multiple sources. Self-reported information on medication use during the past year (with prescription/without prescription/with and without prescription/no), medication-related problems (side effects and/or ineffectiveness; yes/no), and previous PGx testing (yes/no) was collected via the T0 questionnaire. Age (years), sex (male/female), and educational level (categorized as low, middle, or high) were retrieved from the Lifelines database. PGx data were used to determine whether participants carried at least one actionable drug-gene interaction, defined as a drug-gene pair for which the DPWG provides a concrete dose recommendation or an alternative therapy.[31]

2.3.4. Acceptance and reasons

Acceptance of the PGx passport was measured using two approaches: 1) PGx passport acceptance among the total invited population, and 2) PGx passport acceptance among the questionnaire respondents. For both measures, PGx passport acceptance was defined as participants who provided consent to receive their personalized PGx passport results through the smartphone application. Moreover, participants' intention to accept or decline the PGx passport was assessed at T0 with the statement “I intend to accept the offer to receive my pharmacogenetic (PGx) passport”, which participants rated on a 7-point Likert scale ranging from 1 (very unlikely) to 7 (very likely). Participants who indicated an intention to decline the offer (scores 1–3) were subsequently asked to indicate their reasons for declining, using a multiple-choice question with seven predefined response options (specified in Fig. 5) and an additional “Other” option allowing free-text responses. Participants who indicated an intention to accept (scores 4–7) were

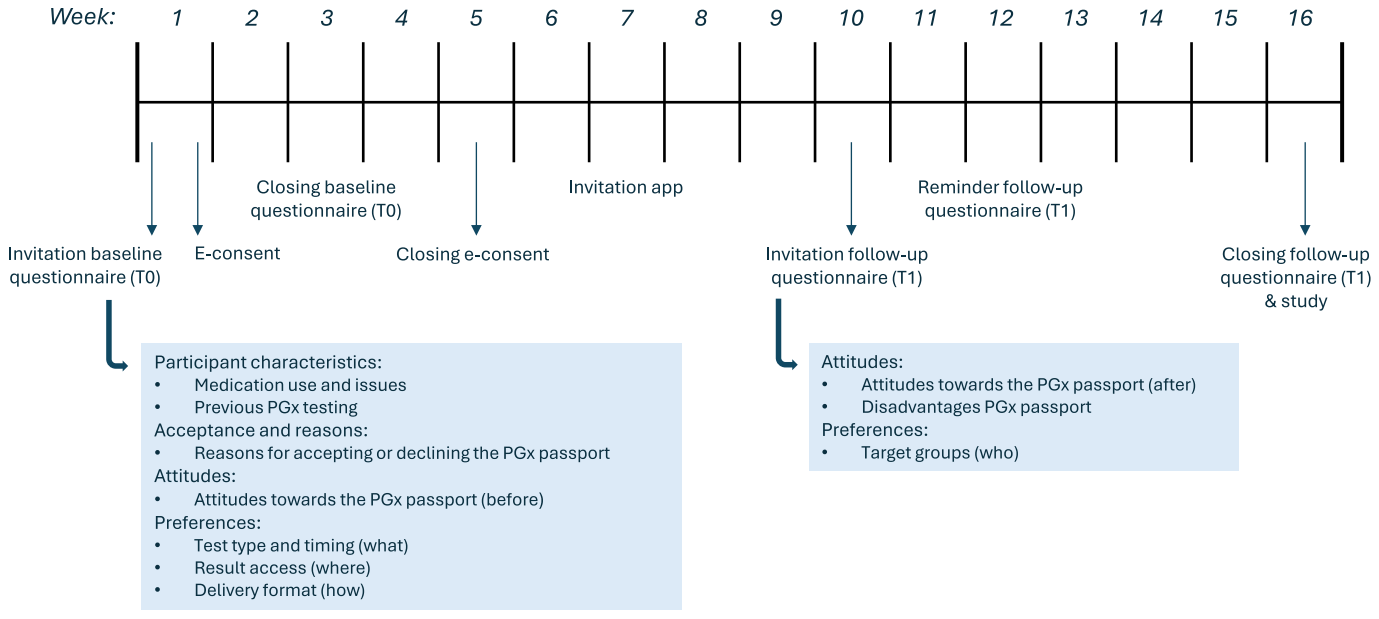

Fig. 2. Study procedure. PGx, pharmacogenetic.

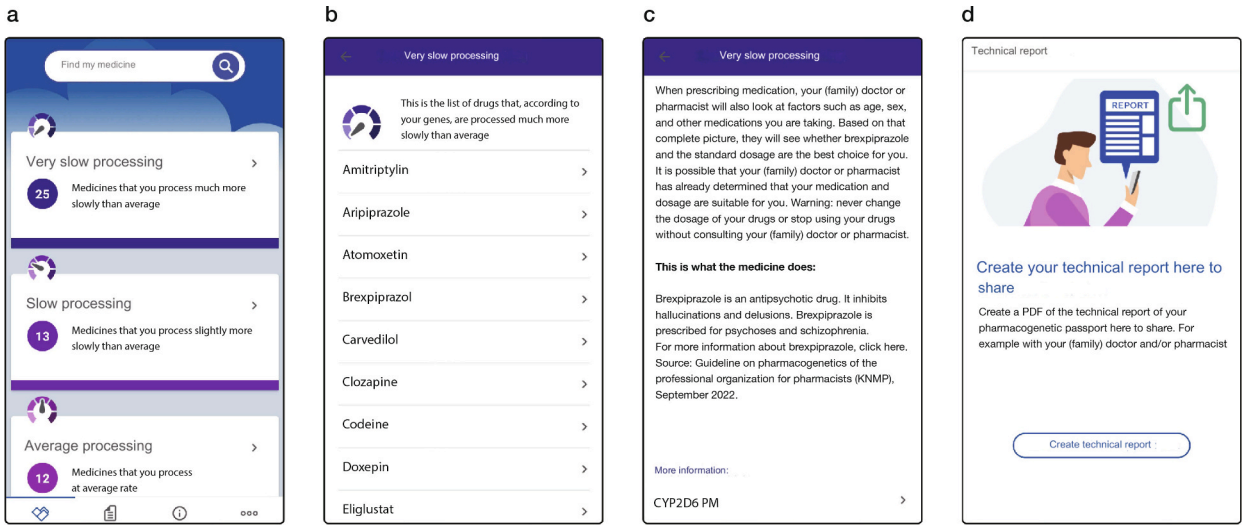

Fig. 3. Overview of the Gen en Geneesmiddel app (translated from Dutch). (**a**) Main menu, where five categories can be selected: poor, intermediate, normal, and ultrarapid metabolism and other processes. (**b**) A personalized list of medications in the poor metabolism category. (**c**) Explanation of the predicted metabolism of brexpiprazole. (**d**) The pharmacogenetic profile can be saved or shared from the app. Reprinted from *American Journal of Human Genetics*, Vol. 112(5), Lanting et al., "Low-cost generation of clinical-grade, layperson-friendly pharmacogenetic passports using oligonucleotide arrays", 1015-1028, 2025, with permission from Elsevier.[28]

asked to report their reasons for acceptance using eight predefined response options (specified in Fig. 5), also with an "Other" option. Next, participants who initially intended to accept the PGx passport were informed that the PGx passport could only be delivered via a smartphone application. Following this information, intention to accept was reassessed using the same 7-point Likert scale. Participants who then selected response options 1–3 were classified as declining the PGx passport due to the app-based delivery method and were asked to indicate their reasons for declining using seven predefined response options (specified in Fig. 5) and an "Other" option. Open-ended responses were summarized by the first researcher (SEW) and subsequently verified by a second researcher (AVR).

2.3.5. Attitudes

Attitudes towards the PGx passport were assessed at baseline (T0) and follow-up (T1), using self-constructed questions based on the Theory of Planned Behavior framework.[33] Participants rated their attitudes on five aspects (perceived importance, reassurance, usefulness, responsibility, and pleasantness) on a 7-point Likert scale (1 = negative, 7 = positive). The mean score across aspects represented overall attitudes, while each aspect was also analyzed separately. To gain more insight into the concerns of participants whose overall attitude had become more negative at follow-up, they were asked to describe their perceived disadvantages of the PGx passport. Open-ended responses were categorized by the first researcher (SEW) and subsequently verified by a second researcher (AVR). Any ambiguities or discrepancies were resolved through discussion. Additionally, participants were asked to rate the likelihood of recommending the PGx passport to others on a scale ranging from 0 (very unlikely) to 10 (very likely).

2.3.6. Preferences

Preferences regarding the PGx passport and PGx testing were assessed using self-constructed items covering four questions corresponding to "what", "who", "where", and "how". At T0, attitudes towards single-gene and multi-gene PGx testing were also assessed within the "what" domain and are presented here alongside preferences for test type and timing. Participants rated these attitudes on the same five aspects (perceived importance, reassurance, usefulness, responsibility, and pleasantness) on a 7-point Likert-scale (1 = negative, 7 = positive) (what). Additionally, participants selected their preferred time and type of PGx test (what) and their preferred method of receiving PGx passport results (how) from predefined response options. Also at T0, participants rated their preferences regarding access to the PGx passport (where) using a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree). At T1, participants indicated which target group they believed should be offered the PGx passport (who) on the same 5-point Likert scale.

2.4. Data analysis

Descriptive statistics were used to summarize the data. The mean and standard deviation were calculated for continuous variables, and frequencies and percentages for categorical variables. For subgroup analysis, the Chi-square test was used to compare proportions between groups for categorical variables. For continuous variables, the Welch's *t*-test was employed to compare means between two independent groups, allowing for unequal variances. When data were not normally distributed, the Wilcoxon signed-rank test was used for paired or related samples.

The importance, usefulness, and pleasantness items were reverse-coded for attitudes towards the PGx passport at T0 and T1 and towards single-gene and multi-gene testing at T0, so that higher scores consistently indicated more positive attitudes. Additionally, responses on 7-point Likert scales were categorized as negative (1–2), neutral (3–5), or positive (6–7), with a strict threshold for the positive category to enhance clarity and interpretive impact of the findings. A p-value $<$ .05 was considered statistically significant. Effect sizes (r) were calculated for the Wilcoxon signed-rank tests, with r values interpreted as small ($<$ 0.3), moderate (0.3–0.5), and large ($>$ 0.5). Considering the large sample size, both statistical significance and practical relevance were considered when interpreting the results. Additionally, a Bonferroni correction was applied to adjust for multiple comparisons and control the risk of Type I error. All statistical analyses were conducted using R (version 4.4.3).

3. Results

3.1. Participant characteristics

Table 1 presents the participant characteristics. Out of the 4344 eligible participants, 1178 completed the baseline questionnaire

(response rate 27.1%). Participants had a mean age of 58 years and the majority were female. Nearly half of the participants had a high educational level. In the past 12 months, 31.7% of participants reported using only prescription medication, 13.8% only non-prescription medication, and 39.5% both, while 15% reported no medication use. Medication-related side effects and/or ineffectiveness were reported by 64.4%, and 1.5% had previously undergone PGx testing.

3.2. Acceptance and reasons

A total of 995 participants accepted the PGx passport offer. This resulted in the following acceptance rates: 1) acceptance among the total invited population was 22.9% (995/4344), and 2) acceptance among the study respondents was 84.5% (995/1178) (Fig. 4).

Fig. 5 illustrates the reasons for accepting or declining the PGx passport. The most frequently reported reason for acceptance was the reassurance of knowing whether certain medications might be ineffective for them (73.6%) (Fig. 5a). Participants who declined the PGx passport because it was offered via an app stated that their main reasons were not wanting an app for this purpose (47.3%) and privacy concerns (43.2%) (Fig. 5b). Finally, the most common reasons to decline the PGx passport in general were not having a need for it (32%) or not being interested in the information (24%) (Fig. 5c). Open-ended question responses that did not match the predefined answer options can be found in Supplementary Material 1.

3.3. Attitude towards the PGx passport

General attitudes towards the PGx passport at baseline and follow-up are presented in Fig. 6. At baseline, 75.9% of all participants reported a positive attitude (scores 6–7). Those who accepted the PGx passport and completed the follow-up questionnaire were the most positive (78.7% and 79.4%, respectively). However, among participants who completed follow-up, overall attitude scores decreased significantly from baseline to follow-up, although the effect was small ($p = .007$, $r = 0.11$) (Fig. 6a). Ratings of importance ($p < .001$, $r = 0.21$) and usefulness ($p = .003$, $r = 0.12$) showed similar small decreases (Fig. 6b). No significant differences were observed for perceived reassurance ($p = .105$), responsibility ($p = .605$), and pleasantness ($p = .855$). Among participants whose average attitude score across the five aspects (i.e., perceived importance, reassurance, usefulness, responsibility, and pleasantness) declined from baseline to follow-up, three primary concerns were identified in participants' open-ended responses: 1) privacy and data security, including hacking and data breaches, 2) misuse by insurers or other third parties, including fears that the information could be used to identify costly patients or restrict access to insurance, and 3) worries and anxieties regarding the results. Other concerns are detailed in Table S1 in Supplementary Material 2. Moreover, respondents rated their likelihood of recommending the PGx passport to others with an average score of 8.7/10.

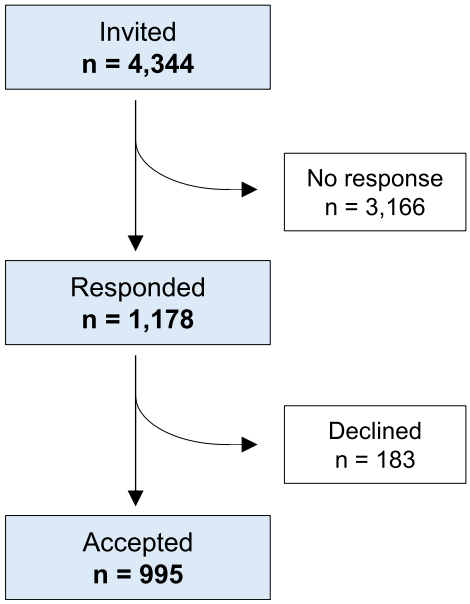

Fig. 4. Flow diagram showing the number of invited participants, respondents, and those who accepted and declined the pharmacogenetic passport.

Table 1
Demographic, social and health characteristics.

	Total ($n = 1178$)	Accepted ($n = 995$)	Declined ($n = 183$)	Acceptance rate (%)	Statistic (df)	p value
Age (years)[1]	57.8 ± 12	57.4 ± 12	59.9 ± 12	84.5%	−2.57 (254.33)	**0.011***
Sex[2]					2.53 (1)	0.111
Female	720 (61.1%)	598 (60.1%)	122 (66.7%)	83.1%		
Male	458 (38.9%)	397 (39.9%)	61 (33.3%)	86.7%		
Education[2, a]					20.04 (2)	**< 0.001*****
Low	109 (9.9%)	82 (8.8%)	27 (16.6%)	75.2%		
Middle	470 (42.9%)	387 (41.5%)	83 (50.9%)	82.3%		
High	517 (47.2%)	464 (49.7%)	53 (32.5%)	89.7%		
Self-reported medication use past 12 months[2]					9.52 (3)	**0.023***
With prescription	373 (31.7%)	313 (31.5%)	60 (32.8%)	83.9%		
Without prescription	163 (13.8%)	140 (14.1%)	23 (12.6%)	85.9%		
With and without prescription	465 (39.5%)	405 (40.7%)	60 (32.8%)	87.1%		
No	177 (15%)	137 (13.8%)	40 (21.9%)	77.4%		
Self-reported side effects and/or ineffectiveness[2]					5.86 (1)	**0.015***
Yes	759 (64.4%)	656 (65.9%)	103 (56.3%)	86.4%		
No	419 (35.6%)	339 (34.1%)	80 (43.7%)	80.9%		
Ever had PGx test[2, b]					5.89 (1)	**0.015***
Yes	18 (1.5%)	11 (1.1%)	7 (3.8%)	61.1%		
No	1159 (98.5%)	983 (98.9%)	176 (96.2%)	84.8%		
≥ 1 actionable drug-gene interaction[2]						
Yes	N/A	92%	N/A	N/A	N/A	N/A
No	N/A	8%	N/A	N/A	N/A	N/A

[a] 82 missing values, [b] 1 missing value. Options for 'Ever had a PGx test' and 'Side effects and/or ineffectiveness' were grouped yes (yes/probably) and no (no/probably not). Abbreviations: df, degrees of freedom, PGx, pharmacogenetic.

[1] mean ± sd (Welch's t-test).

[2] n (%) (Chi-square test) with significance levels: * $p < .05$, ** $p < .01$, *** $p < .001$.

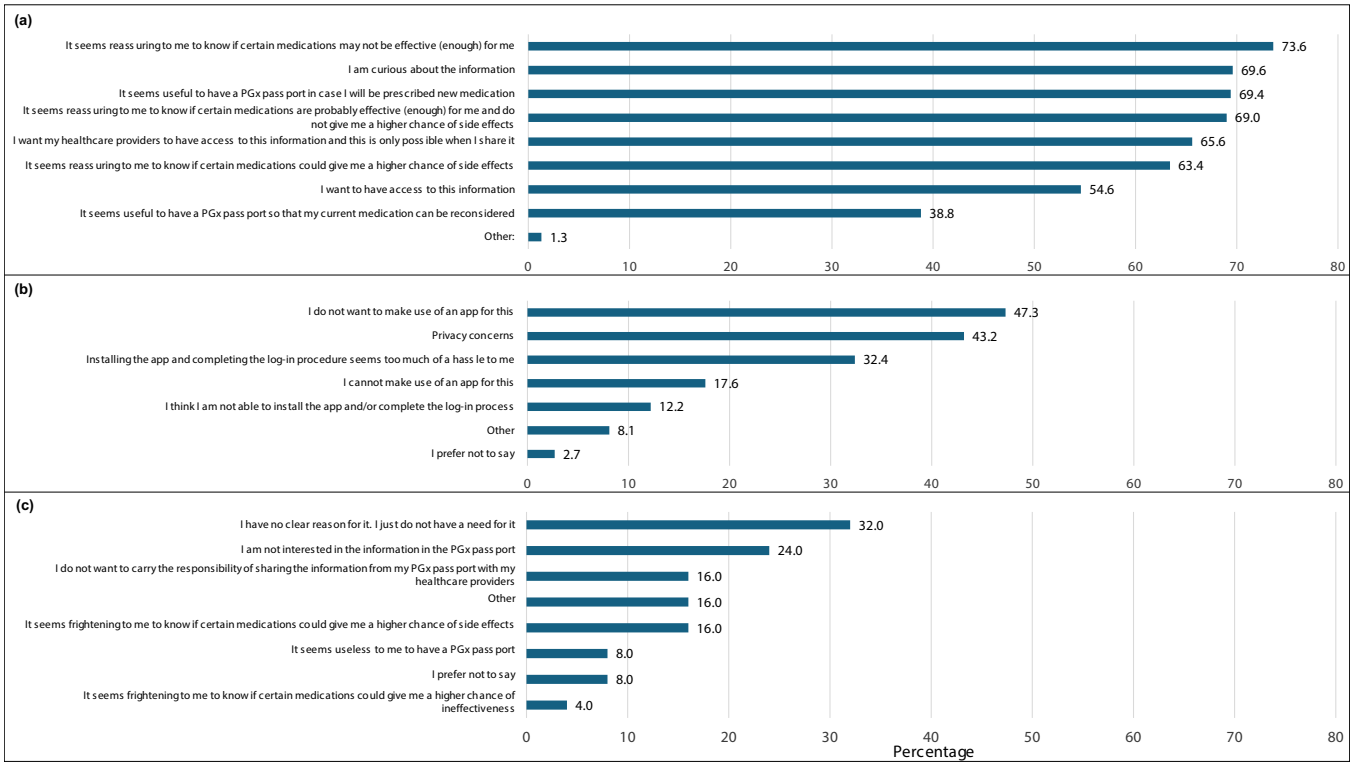

Fig. 5. (**a**) Reasons for accepting the PGx passport ($n = 1153$). (**b**) Reasons for declining the PGx passport via an app ($n = 74$). (**c**) Reasons for declining the PGx passport in general ($n = 25$). Participants could select multiple responses; percentages therefore do not sum to 100%. PGx, pharmacogenetic.

3.4. Preferences for PGx testing

Firstly, participants were asked which groups should receive the PGx passport (who) (Fig. 7a). Most participants supported offering the PGx passport to all individuals. However, support was significantly higher when participants rated medication users ($p < .001$, $r = 0.38$) and patients receiving specialist care ($p < .001$, $r = 0.39$), with moderate effect sizes.

Secondly, participants rated their attitudes towards single-gene and multi-gene PGx testing and indicated their preferences for test type and timing (reactive, pre-therapeutic and preemptive) (what). Participants were significantly more positive about single-gene compared to multi-gene testing, but with a small effect size ($p = .029$, $r = 0.06$) (Fig. 7b). At the same time, most participants preferred preemptive multi-gene

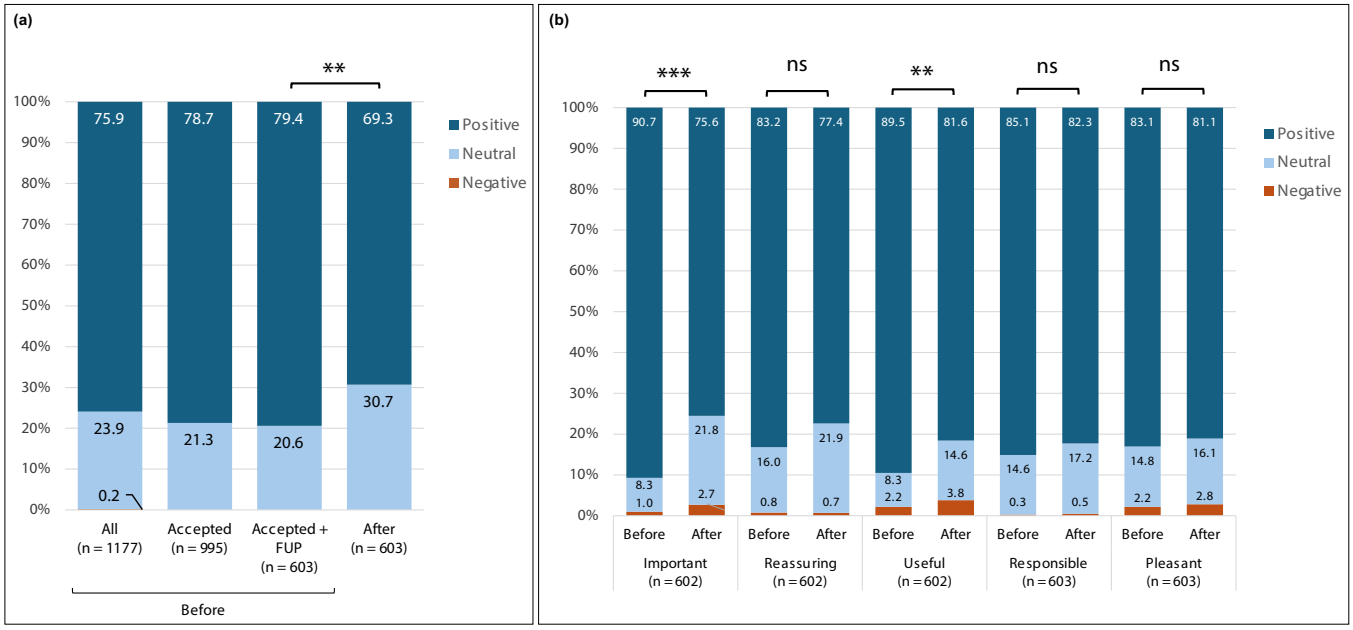

Fig. 6. Attitude scores at baseline and follow-up. (a) Mean attitude scores. (b) Attitudes per aspect. Scores are derived from a 7-point Likert scale and have been categorized into negative (1–2), neutral (3–5), and positive (6–7) responses. Values represent percentages of participants per response category. Wilcoxon signed-rank test with significance level: *** $p < .001$ and ** $p < .01$. PGx, pharmacogenetic, FUP, follow-up, ns, not significant.

testing to a pre-therapeutic single-gene test (Fig. 7c).

Thirdly, participants were presented with two statements regarding access to their PGx passport (where). Significantly more participants preferred exclusive personal access over sharing it directly with their healthcare professionals, although the effect size was small ($p < .001$, $r = 0.14$) (Fig. 7d).

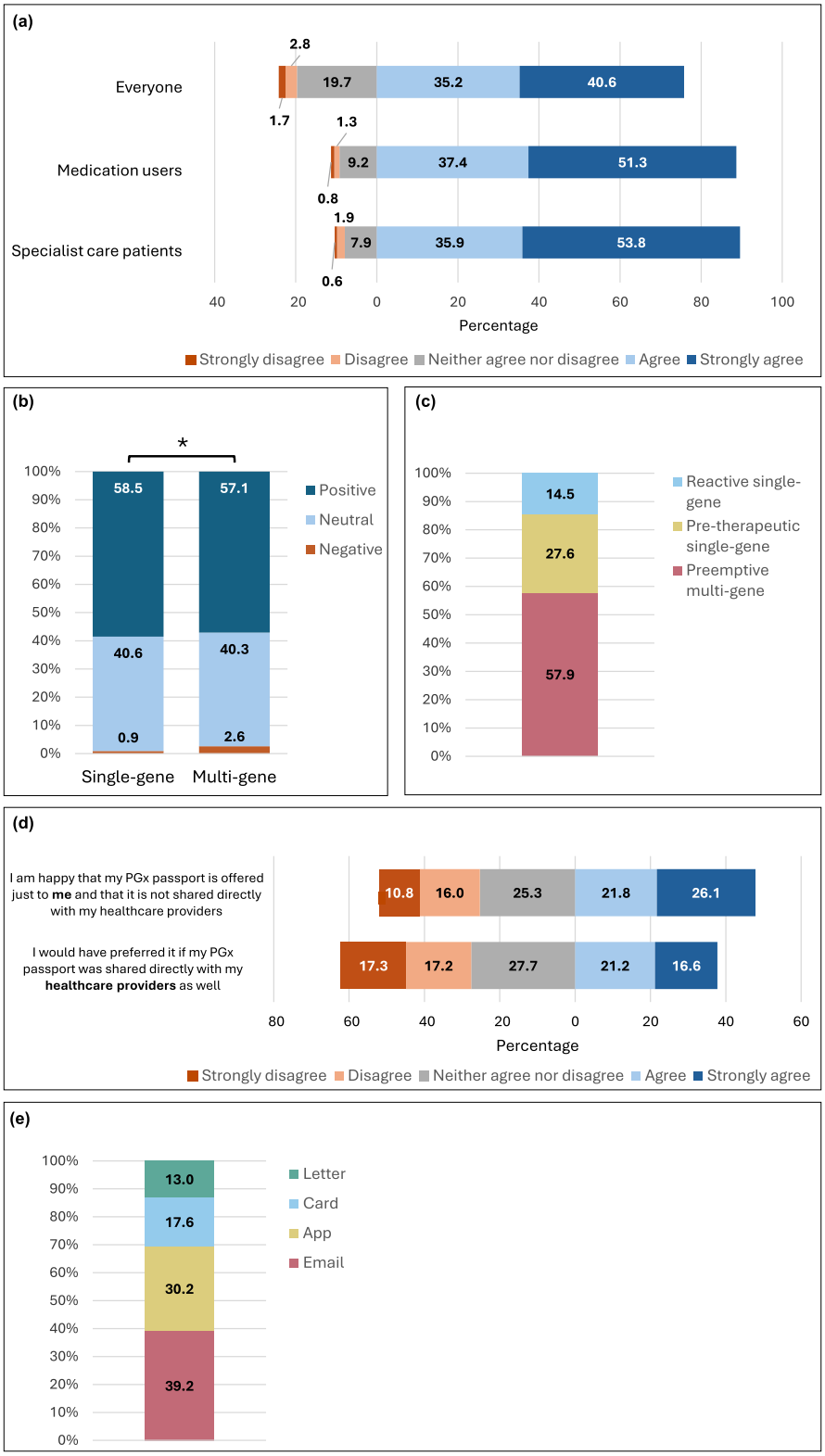

Fig. 7. (**a**) Who – preferred target groups for the PGx passport. (**b**) What – attitudes towards single-gene and multi-gene PGx testing. (**c**) What – preferred PGx test type and timing. (**d**) Where – preferred access to PGx passport results. (**e**) How – preferred delivery format for the PGx passport. Scores for (a) and (d) are derived from a 5-point Likert scale, centered at neutral (0). Score for (b) was derived from a 7-point Likert scale and categorized into negative (1–2), neutral (3–5), and positive responses (6–7). Values represent percentages of participants per response category. Wilcoxon signed-rank test with significance level: * $p < .05$. PGx, pharmacogenetic.

Finally, participants were asked how they would like to receive their PGx passport (how). Email was the most frequently preferred delivery format, followed by an app, with fewer participants selecting a physical card or printed letter (Fig. 7e).

4. Discussion

In this study, we aimed to evaluate acceptance, attitudes, and preferences of the general population regarding a personal preemptive multi-gene PGx passport and PGx testing. Firstly, acceptance among study respondents was high. However, overall participation in the study was low, though consistent with response rates in Lifelines studies. Nevertheless, selection effects cannot be excluded, as individuals more interested in, or accepting of, PGx testing may have been more likely to participate. Secondly, most participants reported highly positive attitudes towards the PGx passport, although these declined slightly at follow-up. Thirdly, participants generally supported offering the PGx passport to most people, with particularly strong support for medication users and patients in specialist care. Fourthly, single-gene testing was viewed more positively than multi-gene testing, yet paradoxically, most participants preferred preemptive multi-gene testing. Finally, participants favored personal control over result access and preferred receiving their PGx passport digitally rather than via physical formats. It is important to note that most observed effects were small, although they may still be meaningful at the population level.

High acceptance of the PGx passport among study respondents corresponds to their strongly positive attitudes. The most frequently reported reason, that the PGx passport offered reassurance by helping identify potentially ineffective medication, aligns with findings from the US general population. In the survey, 92% expressed interest in PGx testing to help select the most effective medication.[20] Similarly, a UK population survey found that improved medication effectiveness was more often reported as a reason for testing than a reduced risk of ADRs (72% versus 63%).[22] Another commonly mentioned reason in our study was that the passport could prove valuable for future prescriptions, whereas its use for reconsidering current treatment was reported considerably less often. This is consistent with the preventive rationale of preemptive multi-gene PGx testing. Respondents who declined the PGx passport were primarily concerned with app delivery and privacy. Even among participants who accepted the passport, privacy and data safety remained their main concern. Similar privacy concerns have been reported in a study showing reluctance to undergo testing when DNA samples or results might be shared without consent.[20]

Participants' attitudes towards the PGx passport were largely positive, indicating openness to the concept of PGx testing. Ratings were generally consistent across dimensions of perceived importance, reassurance, usefulness, responsibility, and pleasantness. Perceived usefulness in our population (89.5%) was slightly lower than the 92% reported among Dutch patients, possibly reflecting the absence of immediate medication needs.[15] This may also explain the decline in perceived usefulness and importance after receiving their PGx passport, as participants without a direct clinical need may have reassessed its relevance. A small proportion of participants expressed concerns that the PGx information could increase worries or anxieties regarding current medications. Similarly, in an Estonian biobank study, 5% of participants considered the PGx section of their genomic report scary.[34] Observations from US primary care also indicate that PGx results can reduce confidence in existing prescriptions, particularly among patients with lower perceived understanding.[35] This highlights the need to present PGx results as information that can guide, rather than determine, treatment decisions, and to discuss their meaning with healthcare professionals before medication changes are made. Despite these concerns, participants' overall recommendation score of 8.7/10 underscores their strong and broadly positive attitudes towards the PGx passport.

Our findings showed a clear preference for preemptive testing, with the majority favoring preemptive multi-gene testing over reactive or pre-therapeutic single-gene testing. However, when asked about attitudes towards single- versus multi-gene testing, participants expressed slightly more positive attitudes towards single-gene testing. This may reflect the relative immediacy of single-gene testing, as it is easier to understand and directly linked to a prescribing decision. In contrast, multi-gene testing is more complex and abstract, potentially challenging participants' understanding or raising concerns about the breadth of DNA analysis. Nevertheless, the practical relevance of the difference between single- and multi-gene testing is likely limited, as the large sample size may have contributed to statistically significant but small effects. The overall preference for preemptive testing may be perceived as more comprehensive and valuable for future treatment decisions, even if it initially provokes concerns. This is consistent with previous findings in primary care, where patients often supported preemptive testing but sometimes struggled to fully grasp its meaning.[24]

Mixed results were also observed regarding participants' preferences for who should have access to their PGx results, with slightly more participants favoring exclusive personal access. These findings are consistent with previous research showing that patient control is highly valued.[36] At the same time, more than one-third of participants preferred direct sharing of their results with healthcare professionals. In a Flemish population survey, 69.2% of participants preferred direct availability of their PGx results to healthcare professionals, while 48% also wished to retain control over which healthcare professionals could access them.[37] These preferences may reflect a wish to decide who can access their results, rather than an unwillingness to share them with healthcare professionals. Clinical use requires that results are available when treatment decisions are made, but this can also be achieved through sharing with patients' permission. Relying on patients to communicate their results may nevertheless be challenging, as previous research shows that patients may have limited awareness or understanding of their PGx results.[38] The preference for exclusive personal access may be related to concerns about privacy, data security, or misuse, but further research is needed to clarify the underlying reasons.

The method of result delivery and the choice of target groups are both crucial considerations for the successful implementation of PGx testing, as they affect comprehension and perceived relevance. Our findings indicate a clear preference for digital formats, which allow for a more detailed and interactive presentation than paper-based formats, particularly for complex topics such as PGx testing.[38] Regarding target groups, who to test remains an ongoing debate.[4] While participants in our study generally viewed population-wide testing as valuable, they prioritized medication users and patients receiving specialist care. This prioritization was also observed in the UK, where 85% of respondents thought that PGx testing should be offered to people taking multiple medications, compared with 58% who supported offering testing to everyone.[22] This aligns with the notion that preemptive testing is particularly beneficial for individuals with chronic conditions, who are more likely to require multiple medications over time.[4]

Collectively, these findings indicate that most participants from the general population are open to PGx testing, which is encouraging for future implementation. However, positive attitudes should be interpreted cautiously, as the high non-response (72.9%) may reflect lower willingness in the broader invited population. The slight decline in attitudes after receiving the PGx passport highlights the importance of setting realistic expectations and clearly communicating its clinical relevance, which may also help mitigate the worries and anxieties reported by some participants. Concerns were mainly related to digital privacy and data security, emphasizing the need for transparent communication and careful handling of genetic data to build public trust and support long-term adoption. Allowing individuals personal control over the sharing of their genetic data may further strengthen trust and autonomy. Participants also preferred receiving their PGx passport in a digital format, which may facilitate such control and is essential for implementation at a large population scale.[34] Given the particularly strong support for offering PGx testing to medication users and patients

receiving specialist care, these groups may represent suitable initial target populations for implementation. Although PGx passports are ultimately intended for the broader population, a phased implementation starting with these groups may be both more feasible and clinically relevant. An additional consideration is who bears the cost of testing. In the Netherlands, PGx testing may be reimbursed when clinically indicated, whereas population-wide preemptive panel testing is not routinely covered. Broader implementation will therefore require sustainable reimbursement, particularly as evidence for the cost-effectiveness of panel-based PGx-guided prescribing continues to grow.[39]

4.1. Strengths & limitations

This study has several strengths. First, the PGx passport was actively offered rather than assessed through hypothetical scenarios, providing real-world insights into participants' views and experiences. Second, the use of a population-based cohort supports the relevance of preemptive PGx testing beyond clinical populations.

However, the study also has limitations. Although recruitment through Lifelines extended the study beyond clinical patient populations, respondents were older, more often female, and more highly educated than the general population, based on national statistics.[40,41] Selection for the genotyped subcohort was restricted to individuals of "Caucasian ancestry", further limiting generalizability.[27] Also, participants were recruited from the Lifelines UGLI subcohort and had already consented to genotyping for general research purposes. This did not indicate a prior decision to undergo PGx testing, but these participants may nevertheless have been more receptive to genetic testing than the general population. Furthermore, respondents may have been more interested in PGx or more engaged with healthcare than non-respondents, potentially leading to more favorable findings. Additionally, the digital offer and questionnaire may have limited participation of people with lower digital literacy. Finally, medication-related adverse effects and ineffectiveness were self-reported and were not clinically verified. These reports therefore reflect participants' perceived experiences and may be subject to recall or attribution bias.

5. Conclusion

This population-based cohort showed broad support for the PGx passport, primarily driven by the reassurance it provides in identifying potentially ineffective medication. However, preferences regarding its content and form varied. Most favored preemptive PGx testing, digital delivery, and personal control over sharing their results. Participants also expressed concerns about privacy, data security, and possible anxiety about their results. These concerns highlight the importance of clear communication and safeguards for privacy and data security. Enhancing PGx knowledge may further support informed decision making and help manage expectations.

Declaration of generative AI use

During the preparation of this work the author(s) used Claude (Anthropic) and ChatGPT (OpenAI) in order to assist with language editing, restructuring of text, and refinement of the manuscript. After using these tools, the author(s) reviewed and edited the content as needed and take (s) full responsibility for the content of the published article.

CRediT authorship contribution statement

S.E. Westervoorde: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **J. Niebuur:** Writing – review & editing, Project administration, Methodology, Investigation, Conceptualization. **J.A.M. Dekens:** Writing – review & editing, Supervision. **J. Slager:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **P. Lanting:** Writing – review & editing, Methodology, Conceptualization. **M. Plantinga:** Writing – review & editing, Supervision, Methodology, Conceptualization. **I. Christiaans:** Writing – review & editing, Supervision, Methodology, Conceptualization. **A.V. Ranchor:** Writing – review & editing, Supervision, Methodology, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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