Investigating Patient Acceptability of Stratified Medicine for Schizophrenia: A Mixed Methods Study

Sagar Jilka*,1,2,0, Clarissa Mary Odoi^{1,2}, Sazan Meran¹, James H. MacCabe^{1,2}, and Til Wykes^{1,2}

¹Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; ²South London and Maudsley NHS Foundation Trust, London, UK

*To whom correspondence should be addressed; Institute of Psychiatry, Psychology & Neuroscience, King's College London, Henry Wellcome Building, 16 De Crespigny Park, London SE5 8AF, UK; tel: 0044 207 848 0219, e-mail: sagar.jilka@kcl.ac.uk

Background: Health services have advocated a stratified medicine approach in mental health, but little is known about whether service users would accept this approach. Aims: To explore service users' views of the acceptability of stratified medicine for treatment-resistant schizophrenia compared to the traditional "trial-and-error" approach. Methods: A mixed methods observational study that explored questionnaire responses on acceptability and whether these responses were affected by demographic or clinical variables. We also investigated whether treatment responsiveness or experience of invasive tests (brain scans and blood tests) affected participants' responses. Questionnaire generated qualitative data were analyzed thematically. Participants (N108) were aged 18-65, had a diagnosis of schizophrenia, and were adherent to antipsychotic medication. Results: Acceptability of a stratified approach was high, even after participants had experienced invasive tests. Most rated it as safer (62% vs 43%; P < .01[CI: -1.69 to 2.08]), less risky (77% vs 44%; P < .01 [CI: -1.75 to 1.10]), and less painful (90% vs 73%; P < 0.01[CI: -0.84 to 0.5]) and this was not affected by treatment responsiveness or test experience. Although not statistically significant, treatment nonresponders were more willing to undergo invasive tests. Qualitatively, all participants raised concerns about the risks, discomfort, and potential side effects associated with the invasive tests. Conclusions: Service users were positive about a stratified approach for choosing treatments but were wary of devolving clinical decisions to purely data-driven algorithms. These results reinforce the value of service user perspectives in the development and evaluation of novel treatment approaches.

Key words: mental health/precision psychiatry/adult psychiatry/treatment-resistant schizophrenia/neuroimaging

Introduction

Health services and research funders have advocated a stratified medicine approach in mental health.¹⁻³ Stratified medicine refers to the use of tests that predict treatment response to drive treatment decisions for individual patients.⁴ This approach relies on biomarkers that can be used to tailor treatment choices and thus improve effectiveness, and/or minimize adverse drug effects. One group of medications, antipsychotics, has benefits for people with psychosis but around one-third of individuals show little response. There is indication for an increased capacity to synthesize dopamine in those individuals who respond to treatment⁵ while in those who do not respond, there is an increased synthesis of glutamate.⁶ These differences can be measured by means of positron emission tomography (PET) and magnetic resonance imaging (MRI),^{7,8} although these methods are currently restricted to research questions. Other potential markers have been identified from standardized cognitive and psychological measures. A combination of these biological and psychological tests may provide the most effective stratification. But such a complex and lengthy set of assessments need to be acceptable to service users if they are to be easily implemented into services.

Views on the trial-and-error approach to current prescribing, and concerns about the procedures involved in a stratified approach, have been highlighted in a previous study with participants who discussed these issues hypothetically in qualitative focus groups. 10 The current study builds on this previous work by exploring service user opinions in more depth and focuses on a specific exploration of their concerns, views of acceptability, and how this new approach compares with the traditional trial-and-error approach to prescribing medication.

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Our study is motivated by 3 main questions: (1) how service users think their doctor chooses their medication, (2) what concerns they have about stratified medicine, and (3) their acceptability of a stratified approach and of different types of tests. We are also interested in whether characteristics such as treatment response, age, ethnicity, length of time in contact with services, symptom severity might moderate their views, as these factors have been associated with attitudes toward medication and treatment choices 11,12-14. Rather than asking people about acceptability when individuals had no immediate prospect of experiencing these tests, we embedded our investigation in an observational study (Schizophrenia: Treatment Resistance and Therapeutic Advances [STRATA]) on the response to nonclozapine antipsychotics.

Methods

Design

This is a mixed methods study using the self-report Stratified Medicine Questionnaire (SMQ, described below in measures). The STRATA study was entirely observational with participants' medication not changing during the study. The STRATA study^{6,15} was designed to test the hypothesis that there is an increased capacity to synthesize dopamine in individuals who respond to treatment⁴ while in nonresponders there is an increased synthesis of glutamate. Participants could receive 4 tests—cognitive, blood, and imaging (PET and magnetic resonance spectroscopy [MRS]) whose order depended on neuroimaging availability and scheduling and participant preferences. Participants could answer the SMQ before or after the invasive tests (PET, MRS, and blood tests), which allowed us to investigate whether their preferences change as a result of experiencing them. We also investigated whether treatment responsiveness (described below) affected attitudes. SMQ completion took place after written consent and ethical approval was granted by the Oxford Research Ethics Committee (ref: 15:/LO/0038). The STRATA official (https://www.kcl.ac.uk/ioppn/depts/ps/research/strata) provides more detail.

Participants and Recruitment

Participants were included if they were: 18–65 years old, had a DSM-5 diagnosis of schizophrenia or schizophreniform disorder (Mini International Neuropsychiatric Interview¹⁶), were adherent to antipsychotic treatment (score of >3 Clinician Rating Scale¹⁷), have completed the SMQ, and be classified as either a treatment responder or nonresponder. Demographic information, antipsychotic medication history, and treatment response were completed by interview and supplemented by medical records.

Participation in MRI scans required the exclusion of those who had severe claustrophobia or contraindications for MRI.

Participants were grouped into the following samples based on National Institute of Health and Care Excellence's (NICE) definition of treatment response¹⁸:

Sample 1: Responders vs Nonresponders.

Treatment responsive:

- (i) Previous treatment with only 1 antipsychotic drug since onset, or treatment changes were due to adverse effects not for nonresponse
- (ii) Clinical Global Impression-Schizophrenia (CGI-SCH) severity score of <4
- (iii) Positive and Negative Syndrome Scale (PANSS) total <60¹⁹

Treatment nonresponsive:

- (i) Previous documented treatment with at least 2 antipsychotics each above the minimum therapeutic dose as defined by the British National Formulary (BNF) for >4 weeks each
- (ii) Despite ongoing treatment and adequate adherence, a CGI-SCH severity score of >3
- (iii) PANSS score total severity rating of at least 70

Sample 2: Before vs After Invasive Tests. This was a smaller group as not all tests were available at each recruitment centre. To be included, participants had to have completed all the invasive tests (PET, MRS, blood tests) either before completing the SMQ (before all tests group), or afterwards (after all tests group).

Measures

- (i) Demographic (age, gender, and ethnicity), and clinical data (PANSS, ¹⁹ and service use) were collected
- (ii) Stratified Medicine Questionnaire (SMQ)

The SMQ was developed specifically for this study through participatory methods as described by Rose et al.²⁰ Themes were identified in service user and carer focus groups on the topic of stratified medicine¹⁰ and they formed the basis for the items. Items were then reviewed in several patient advisory groups to ensure they were understandable and feasible for our participants. As items referred to the 4 different test types, we provided descriptions of each test to ensure all participants understood what each test entailed irrespective of whether they had had previous experience. A copy of the SMQ is provided in supplementary material.

The questionnaire consists of 9 items: 4 free-text and 5 multiple-choice questions. The free-text items explored (1) how participants thought their doctors currently choose their antipsychotic medication, (2) their concerns

about stratified medicine, (3) what would make stratified medicine more useful or acceptable, and (4) their concerns about participating in the stratified medicine clinical trial.

In the first multiple-choice question, participants chose which words applied to stratified medicine and/or the current approach. The 4 choices were: "safe," "painful," "convenient," and "risky." Although the total acceptability score for these words and the score on "whether you would be happy for your doctor to use stratified medicine" item were positively correlated suggesting validity, we decided to consider each word separately as Cronbach's alpha for total scores was low for views on the current and stratified medication approaches (.579 and .474, respectively) suggesting that responses to each word were relatively independent.

The final 4 multiple-choice questions were:

- Would you be happy with your doctor using stratified medicine? (Yes/No/Don't know)
- How likely are you to participate in each of 4 tests in routine clinical care—(i) interview and cognitive tests; (ii) blood (genetics) test; (iii) MRI-type scan (MRS); and (iv) PET scans, all answered on a 5-point Likert scale (not at all likely to very likely).
- Would you be willing to participate in a randomized controlled clinical trial (where their current medication could be affected) to test the stratified medicine approach? (Yes/No/Don't Know)
- What further information would you require to decide to take part in a trial? (choosing one or more from medical/scientific information, firsthand experience/reassurance, or other [free choice]).

Data on the SMQ were collected in person by graduate research assistants between March 2015 and February 2017 either before or after experiencing invasive tests. This procedure depended on patient preference and availability of invasive procedure scheduling (eg, scanner time).

Analyses

We first characterized our sample using descriptive statistics and tested representativeness by investigating whether those included in our study differed from those excluded on sociodemographic and clinical data using chi-square or *t* tests where appropriate.

We compared sociodemographic and clinical data between (1) participants who were treatment responsive against those non responsive (sample 1), and (2) participants who completed the SMQ before experiencing invasive tests against those completing it afterwards (sample 2), using chi-square or *t* tests.

Qualitative Analyses. The qualitative analyses focused on responses to the 4 free-text items which investigated how participants thought their doctors currently choose

their antipsychotic medication, their concerns about stratified medicine, about participating in a clinical trial, and what would make stratified medicine more acceptable. We adopted an inductive, exploratory framework analysis, ²¹ where 2 researchers (C.O. and S.M.) independently identified themes from the free-text responses and constructed a thematic framework. A consensus was reached for the final codes, and the framework generated was applied systematically to all the free-text responses using NVivo 11.²² A detailed breakdown of our qualitative methodology is provided in the supplementary information, methods section.

Quantitative Analyses. We investigated the acceptability of stratified medicine through the 5 multiple-choice questions, which were analyzed using IBM SPSS Statistics 24.0. We performed logistic regression analyses where the independent variables are participant's views, and the dependent variables are demographic and clinical characteristics (using median splits on age, duration service contact, symptom severity, White/Black and Minority Ethnic (BAME) grouping for ethnicity, and responder status [treatment responsive or not]). We report the proportion of participants who (1) would be happy for their doctor to take a stratified medicine approach, (2) would be interested in taking part in a future clinical trial of stratified medicine, and (3) want medical/scientific information, or firsthand experience/reassurance before they enter into a stratified medicine trial. We also investigate whether participants characteristics, response to treatment, or experience of invasive tests influenced their views.

We report the overall proportion of participants willing to undergo PET scans, MRI scans, blood tests, and cognitive tests in routine clinical care, and whether response to treatment affected their willingness.

Results

Study Sample

One hundred and eight participants with complete data constituted the total study sample, which is 73% of those taking part in the STRATA study. The majority were men (n = 94, 87%), had an average age of 29.1 years (SD = 8.7), were mostly White (including White Irish, White Other, and White UK; n = 67, 62%) (see table 1), and had 5.12 (SD = 6.75) years of illness and mild-tomoderate levels of symptoms (PANSS total = 69.41, SD = 19.64). Participants included were no different from those excluded on age, ethnicity, age at first contact with clinical services, length of contact with services, age of first psychotic symptoms, duration of first psychotic symptoms to date of consent, and symptom severity, but were for gender $(X^2(1, n = 144) = 4.267, P = .039)$ [CI: -3.94 to 3.54]), with more women in the excluded group (13%: 28%).

Table 1. Participant Clinical History Variables

	Total (<i>n</i> = 108)	Sample 1: Responder Type (n = 108)		Sample 2: Before and After Tests (<i>n</i> = 47)	
		Responders $(n = 55)$	Nonresponders $(n = 53)$	Before All Tests $(n = 22)$	After All Tests $(n = 25)$
Age (years), mean (SD)	29.10 (8.74)	29.2 (9.20)	29 (8.32)	27.63 (6.74)	31.6 (10.99)
Gender (men), $\%$ (n)	87% (94)	87% (48)	87% (46)	91% (20)	80% (20)
Years in full-time education, mean (SD)	13.32 (3.43)	13.36 (3.03)	13.28 (3.83)	13.72 (2.69)	12.88 (4.45)
Ethnicity (White), $\%$ (n)	62% (67)	60% (33)	64% (34)	73% (16)*	8% (2)*
Duration of contact with services (years), mean (SD)	4.75 (6.95)	4.04 (7.41)	5.49 (6.43)	2.82 (2.11)*	8.20 (10.68)*
Age of first psychotic symptoms (years), mean (SD)	23.98 (6.25)	24.25 (6.33)	23.70 (6.21)	23.25 (7.22)	24.36 (4.70)
Duration from first psychotic symptom to date of consent (years), mean (SD)	5.12 (6.75)	4.95 (7.46)	5.30 (6.00)	4.39 (2.73)	7.24 (10.07)
PANSS score, mean (SD)	69.41 (19.64)	54.13 (9.54)*	84.68 (14.57)*	64.73 (19.26)	74.84 (18.06)

Note: PANSS, Positive and Negative Syndrome Scale.

Sample 1: Response to Treatment. Fifty-five participants (51%) were treatment responsive and 53 (49%) were nonresponsive (table 1). These groups were balanced on all demographic and clinical history variables, except as expected, the total PANSS scores of the treatment nonresponders were higher than for responders (t = 12.77, df = 89.7, P < .00, 95% [CI: -35.3 to -25.8]).

Sample 2: Timing of SMQ Completion. Only 47 participants in the total group completed all 4 test types (22 [47%] completed SMQ before experiencing the invasive tests and 25 [53%] after). The average age of this sample was 29.7 years (SD = 9.3), and the majority were men (n = 40, 85%) and White British (n = 18, 38%) (see table 1). The before and after test groups were balanced on all demographic and clinical history variables, although participants who completed the SMO after the invasive tests had spent more time in contact with services (t(26) = 2.47, P = .02 [CI: 9.87 to 0.90]). This sample was similar to the whole group, but sites where all the tests could be completed tended to be in inner cities which had a higher density of BAME patients (62% vs 38% non-White participants; $X^2 = 6.87$, P = .009 [CI: 0.195 to 0.799]).

Qualitative Analysis

How Do You Think Doctors Choose Your Medication?. Most participants thought that psychiatrists currently use a process of trial-and-error when choosing antipsychotic medication: "They have to try something. They don't know what will work on me." However, some thought that doctors use a personalized approach based on the service user's presenting symptoms, and "working together to find the best fit." Some also thought doctors visually inspect a person, and then decided on a medication based on their clinical experience and the patient's medical history.

One participant said: "Assessments visually [sic], history, behaviours, clinical experience." Beyond this, participants were unsure about the current approach. A few suggested that choice is based on research and guidelines "set by pharmaceutical companies," or the popularity of a medication.

What Are Service Users' Concerns About Stratified Medicine and Participating in a Trial?. Participants were concerned that stratified medicine would result in reductions in individualized care and may lack accuracy. This was expressed as a worry that service users' specific presentations would be ignored ("not too sure if doctors would overlook symptoms of individual patients"). There was also a fear that service users could be wrongly categorized and therefore denied medication that may help them ("may be put in a box too early. People might miss out on getting a drug that suits them best"), or not successfully categorized at all ("if it didn't work what would happen"). However, some responders had concerns around the time-consuming nature of stratified medicine ("time consuming may delay prescription") and questioned whether stratified medicine was better than the current approach ("Might be same as [the] current [approach]. Might be no difference"). Nonresponders reported that the procedures involved in finding a medication would be concerning ("length of time in PET scanner," "invasive," "don't like injections," "radiation from PET scans").

All participants repeatedly raised concerns regarding the risks, discomfort, and potential side effects and those who had already received these tests contributed more to this discussion. They worried about experiencing discomfort and being exposed to radiation, calling for improved scanning techniques, eg, "less noise in the MRI" and "no radiation." They were also apprehensive about the consequences of changing medication in case this might

^{*}Indicates a statistically significant difference between scores.

lead to a deterioration in their mental health conditions ("if it goes wrong, that [my] schizophrenia becomes worse") and result in more side effects.

Another theme among those who had undergone all tests was a concern about the **evidence base** supporting stratified medicine. They commented that the approach was "not tested enough" and needed "additional years of research." In contrast, just 1 participant in the "before all tests" group was worried about the evidence base for stratified medicine and wanted to know if there was research supporting the approach.

For those who had received all tests, the **personal effect** of stratified medicine was a central theme. For example, I individual commented that "lots of proof and studies [are needed] to ensure it is as good if not better than current medication with less side effects." Another participant also felt it was important to identify relapse prevention, calling for "something that would help me not ending up in relapse again." Fewer participants completing the SMQ before the tests commented on effectiveness, although one said, "will it be effective, will it help me." Some said that the acceptability of stratified medicine depended on its ability to improve decision-making in people's care and that it might take longer before medication was accessible.

What Would Make Stratified Medicine More Acceptable to Service Users?. The need for transparency regarding the outcomes and effectiveness of stratified medicine was a central theme to improve acceptability. Participants said that "being shown why you have been given a certain med," "knowing success rates," and having "more of an idea about group[s] people fit into" was important. In general, participants expressed a desire for extensive information about stratified medicine, with a need for "more information," "doctors explaining more," and for clinicians to "make sure that I have all the information." One participant also highlighted the importance of involving patients and their carers in decision-making.

Participants noted that more information and real-life case studies would make it more acceptable ("good explanation. history of tablets - side effects," "Summary of information that proved the relationship that people have between symptoms and medications. A summary document that people could relate to," "case studies of people who went through the same process," "Let the patient know, explain how it may help").

Quantitative Analyses

Is Stratified Medicine Acceptable?. Overall, participants thought a stratified approach was significantly safer (62% vs 43%; $X^2(1) = 8.18$, P < .01 [CI: -1.69 to 2.08]), less risky (77% vs 44%; $X^2(1) = 23.76$, P < .01 [CI: -1.75 to 1.10]), and less painful (90% vs 73%; $X^2(1) = 9.94$, P < .01 [CI:

-0.84 to 0.5]) than a conventional approach, and no different in terms of convenience (46% vs 49%, $X^2(1) = 0.17$, P = .68 [CI: -1.75 to 1.69]) (see supplementary table 1). Most participants reported that they would be happy for their doctor to take a stratified medicine approach (84%) and would be interested in taking part in a future stratified medicine trial (93%).

In our logistic regression analyses, we found statistical significance only for views on the risk of the current approach ($\chi^2(6) = 13.68$, P = .03). The model explained 16.2% (Nagelkerke R^2) of the variance, with a percentage accuracy in classification (PAC) of 64.2%. The only significant variable was that White participants were 0.36 times more likely to report the current approach as risky compared to BAME participants (P = .02 [CI: 0.152 to 0.832]). However, 2 other variables also appeared important. In contrast to our hypotheses, for the stratified approach, BAME individuals thought the stratified approach was risky (P = .034 [CI: -5.37 to 4.9]), and older people thought stratified medicine was safer (P = .04 [CI: -4.43 to 4.84]). No other variables affected participant views of risk. Although age and ethnicity had an effect on risk, neither of these variables had affected whether they would take part in a stratified medicine trial as 94% of all participants were willing to take part in a future clinical trial (6% missing data). When asked about information they would like before entering a stratified medicine trial. One-third did not want any further information. Of those that wanted more information, nearly three-quarters wanted more medical or scientific information, and two-thirds wanted more firsthand experience and reassurance, with many choosing both. Some also said they wanted to have more information including the risks involved, payment, and potential side effects.

Does Response to Treatment Affect Acceptability? There were no significant differences in opinions of stratified medicine or the current approach in terms of safety, risk, painfulness, and convenience (see supplementary table 2.1 for data and significance tests).

Does Experience of Invasive Tests Affect Acceptability? Experience of invasive tests did not affect participants' perception of stratified medicine's safety, risk, convenience, or painfulness (see supplementary table 2.2).

Will Participants Agree to Undergo Invasive Tests as Part of a Stratified Approach?. Most participants agreed that they were likely to undergo the tests (PET scan 81%, MRI 94%, blood test 84%, and cognitive tests 93%). Although those participants who were nonresponsive to treatment were more enthusiastic about taking part in the invasive tests for example in

PET scans (57% vs 42%) and MR scans (54% vs. 46%), these differences were not significant (supplementary tables 2.3 and 2.4).

Discussion

We investigated views of stratified medicine using qualitative and quantitative measures in 108 participants with a diagnosis of schizophrenia. These participants although having consented to take part in an observational study were representative of the population of people whose medication might be reviewed and therefore be affected by a stratified medication approach.²³

The acceptability of stratified medicine was high among all participants, with most considering a stratified approach to be safe, not risky, not painful, and relatively convenient—this high level of acceptability did not change when we considered treatment responsiveness or test experience. The majority reported that they would (1) still undergo invasive tests; (2) be happy with their doctors choosing their medication in a stratified way, and (3) would take part in a future stratified medicine clinical trial. Participants who had undergone all test procedures raised more concerns regarding the risks, discomfort, and potential side effects associated with PET and MRS. The nonresponder group were a little more enthusiastic about PET and MRS (although not significantly) and perhaps this was in the hope that they would find a medication that works for them. But the nonresponders did so with the proviso that they still want clear information and evidence of stratified medicine's benefits, and the risks involved with the test types.

There were few clinical or demographic variables that affected participants' views. Older people had a more favorable opinion about stratified medicine. This was contrary to our hypothesis that they would be more conservative and potentially more negative in their views. We have no explanation for this difference which needs further exploration. The correlation between participant age and length of time in contact with services was significant (R = 0.72, n = 108, P < .001), so this result might be explained because older participants' experience of medication benefits and side effects over a much longer period means they are more open to a new approach. The results regarding ethnicity were complex and warrant further investigation, as people identifying as White thought that the current approach was risky, and people identifying as black thought that stratified medicine was risky. Both groups were, however, still in agreement about its acceptability. This differential response by ethnicity needs further investigation, but does suggest that there may need to be some tailoring of the approach when suggesting a stratified approach.

Stratified medicine has the potential to improve quality of life and curtail lengthy and ineffective treatments especially for those who currently experience little benefit. Given this, the general positive response to stratified medicine, and the tests required, is not surprising. Even after experiencing invasive tests, most participants reported that they would still be happy with their doctor choosing medications using a stratified method and taking part in a clinical trial of stratified medicine. The main concern, however, was that a stratified approach would result in an overemphasis on biological symptoms, and less subjective and emotional considerations. Participants also asked to be fully involved in the medication decision including an understanding of the risks and evidence in favor of this approach.

Our findings build on previous work by Rose et al, ¹⁰ who investigated perceptions of a stratified approach through qualitative focus groups in participants who were not enrolled in a neuroimaging study. In Rose's hypothetical study, service users had a strong desire for a stratified approach to be implemented clinically as many felt "disillusioned" about the potential of existing medication to alleviate symptoms. Despite concerns about the length of PET scans and their intrusive nature, most participants in that study agreed that they would take part in a future clinical trial, in the hope that others would not have to go through a trial-and-error method of finding a suitable medication. Our participants expressed similar opinions irrespective of treatment responsiveness, or experience of invasive tests.

Although Rose et al's study highlighted that the cognitive tests might be too challenging, ¹⁰ we found no differences in acceptability of different tests even after they had been experienced in our study. It may be that the prospect of tests is more daunting than they are in practice and that studies that discuss hypothetical situations might overestimate concerns. It is important to note that participants in both studies strongly expressed a desire that human judgment should not be overlooked by a completely stratified, data-driven approach.

Taking a broader view beyond psychiatry, a public dialogue on stratified medicine²⁴ across conditions revealed similar findings to our study. The public wanted honest information about the pros and cons of a stratified approach and did not want it to result in impersonal rigorous testing. Our participants expressed similar sentiments regarding the need for transparency with decision-making, and the importance of not being "put in a box" based on data. The public consultation also highlighted issues with data sharing and concerns with private company involvement, but our participants did not highlight this as an issue. This may be because our work is focused on research, and participants were asked in a novel setting as they took part in a study.

Strengths and Limitations

This is a novel mixed methods study expanding on previous work investigating service user views of stratified

medicine. ¹⁰ However, we carried out this study in a group of British participants who had already agreed to take part in an observational study. This prior consent might have increased acceptability toward stratified medicine and the tests required to implement it. But even with this potential inflation there was still variation in responses depending on treatment responsiveness and some demographic variables.

Not all participants were eligible for all 4 test types as not all sites carried out the PET scanning so that reduced sample with experience of all 4 tests. But, apart from ethnicity, there were few differences between the smaller sample and the total group. We were not able to identify gender differences because the number of women recruited was small (n = 14). This needs to be a focus of new studies on this topic.

Conclusion

Patient and carer views need to be central to developments in stratified medicine to ensure the acceptability of trials and treatment. Future studies should aim to capture diverse patient views on different test types and modalities as some of our results warrant further investigation. Nonetheless, we find that people with schizophrenia and treatment-resistant schizophrenia would welcome a stratified approach, and clinicians should consider how to communicate this to their patients and ensure the patient-clinician relationship is not overlooked in favor of a purely data-driven approach. Although our work shows that there is enthusiasm for a stratified approach in schizophrenia treatment there is still a need for clear information and transparency in decision-making to ensure its successful adoption.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

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Data Availability

Data are available upon reasonable request.

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