ACKR1 genetic testing should be offered before starting clozapine treatment

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Abstract

Clozapine is the most effective therapy for treatment-resistant schizophrenia, although it can cause neutropenia. In many countries, neutrophil count monitoring is mandatory for people taking clozapine, who must remain above a minimum threshold to start and continue treatment. Some people have low neutrophil counts without increased infection risk, caused by a homozygous variant in *ACKR1* and termed *ACKR1*/*DARC*-associated neutropenia (ADAN). When ADAN is confirmed, reduced neutrophil count thresholds are applied to allow people to start and continue clozapine. However, ADAN diagnoses are often missed, resulting in reduced access to clozapine and unnecessary discontinuation. We review the evidence for *ACKR1* genetic testing to rapidly identify ADAN in people taking clozapine. With multidisciplinary input, we recommend internationally relevant test eligibility criteria, comprising pre-emptive and reactive testing strategies, and we conduct a health economic analysis, estimating total cost savings between £42,732 and £727,990 for the UK healthcare system during the first year of testing. Finally, we propose how to integrate these criteria into clinical practice to enable equitable access to clozapine.

Introduction

In many countries, including the UK, USA, and Australia, clozapine is the only licensed therapy for treatment-resistant schizophrenia, defined as people who do not respond to at least two antipsychotic drugs.[1-6] Treatment resistance affects ~30% of people with schizophrenia,[7] and is associated with serious adverse outcomes, including elevated risk of hospitalisation and suicide.[8] Trial comparisons with other antipsychotic drugs show a significantly improved response in treatment-resistant people receiving clozapine,[9-11] and these are supported by numerous observational studies.[12-15] Clozapine is generally considered the *gold-standard* therapy for treatment-resistant schizophrenia.[16]

Clozapine therapy is associated with several adverse drug reactions, including agranulocytosis (also referred to as severe neutropenia), which is a potentially fatal condition where a person's blood neutrophil count falls below $0{\cdot}5 \times 10^9$/L.[1,2] Agranulocytosis occurs in 0·4% of people taking clozapine,[17] while neutropenia ($<1{\cdot}5 \times 10^9$/L) occurs in 3·8% of people, most commonly during the first 12 months of treatment.[18] To avoid agranulocytosis, many health services mandate or recommend routine blood monitoring for people taking clozapine, although monitoring guidelines can vary between countries.[4,19,20] For example, in the UK, both white cell and neutrophil count thresholds are split into a traffic light system (Table 1).[21,22] Before starting clozapine, a person must return a "green" blood result.[21,22] When a person returns a "red" result, clozapine is immediately stopped, and if consecutive blood tests also return a "red"

result, the person is placed onto the Central Non-Rechallenge Database, which indefinitely prevents restarting of clozapine (also referred to as clozapine rechallenge).[21,22] In the USA, neutrophil (but not white cell) count monitoring is recommended but not mandatory, and thresholds are lower than in the UK (Table 1).[23,24] Similarly, lower neutrophil count thresholds have been recommended for many European Union countries to increase access to clozapine.[4] Other examples are summarised in Appendix 1.

A consideration for clozapine prescribing is whether a person has *ACKR1*/*DARC*-associated neutropenia (ADAN; formerly, benign ethnic neutropenia).[1,21,22] People with ADAN have naturally low blood neutrophil counts, but they do not have an increased risk of infection.[25-29] In the UK, ADAN is diagnosed by a haematologist when other potential causes of neutropenia have been excluded.[21,30] When ADAN is confirmed, reduced blood monitoring thresholds are applied in the UK and USA (Table 1),[21-23] as well as several other countries including Canada, Iceland, and Qatar.[20] This usually allows for clozapine to be started, and helps to avoid unnecessary discontinuation.[21,22]

A homozygous variant in *ACKR1* (Atypical Chemokine Receptor 1; c.-67T>C, rs2814778) is considered causal for ADAN, having been robustly identified through several large genetics studies.[31-35] This is known as the Duffy-null genotype, which refers to the Duffy blood group system.[36] The Duffy-null genotype has a global frequency pattern generally restricted to Sub-Saharan Africa and the Middle East,[37] which is likely due to selective pressures as the Duffy-null genotype protects against some types of malaria infection (*ACKR1* gene products are receptors for *Plasmodium vivax* malarial parasite entry).[38] Consequently, the *ACKR1* variant is prevalent in people with African and Middle Eastern ancestry (~80% and ~25%, respectively), but is much less common in other ancestries like European and East Asian (both <1%).[37,39]

The literature suggests ADAN diagnoses are missed or delayed in people taking (or due to start) clozapine, resulting in unnecessary treatment exclusion and discontinuation.[21,22,34,40-43] The consequences of clozapine discontinuation are serious, including risk of symptomatic relapse,[44] hospitalisation,[45] and suicide.[46] A ready solution could be implementing *ACKR1* genetic testing to rapidly identify ADAN in people taking clozapine. In the UK, the Royal College of Psychiatrists has highlighted the potential benefits of *ACKR1* genetic testing,[47] and the Maudsley Prescribing Guidelines in Psychiatry now recommend *ACKR1* genetic testing for all people starting clozapine.[48] However, pharmacogenetics guideline bodies, such as the Clinical Pharmacogenetics Implementation Consortium, do not provide recommendations for *ACKR1* genetic testing, and the test remains unavailable for most people taking (or due to start) clozapine around the world.

We review the evidence for offering *ACKR1* genetic testing to people taking clozapine. In collaboration with experts in haematology, clozapine prescribing, clinical genetics, and health economics, and with lived experience representation from a patient and carer group, we propose internationally relevant test eligibility criteria, and we provide a detailed example of estimated cost savings for the UK healthcare system. Finally, we

propose how these criteria could be integrated into clinical practice to enable equitable access to clozapine.

***Table 1*. Clozapine blood monitoring criteria for the UK and USA.**

Blood monitoring criteria for clozapine, provided by the UK's Medicines and Healthcare products Regulatory Agency[21,22,49] and the US Food and Drug Administration.[23,24] Nationally recommended monitoring thresholds for people taking clozapine with a diagnosis of ADAN are shown. Clinical actions are summarised. ADAN = *ACKR1*/*DARC*-associated neutropenia; ANC = absolute neutrophil count; NA = not available; WCC = white cell count; * = UK monitoring thresholds for ADAN are provided by the clozapine registries as part of a nationally recognised off-licence agreement.

		Standard thresholds ($\times 10^9$/L)	ADAN thresholds ($\times 10^9$/L)	Clinical actions
UK Medicines and Healthcare products Regulatory Agency (mandatory criteria)*	Green	WCC ≥ 3·5 and ANC ≥ 2·0	WCC ≥ 3·0 and ANC ≥ 1·5	The initial blood result must be in this range to start clozapine treatment. Then, continue clozapine treatment and blood monitoring, as per standard protocol.
	Amber	WCC ≥ 3·0 and < 3·5 and/or ANC ≥ 1·5 and < 2·0	WCC ≥ 2·5 and < 3·0 and/or ANC ≥ 1·0 and < 1·5	Continue clozapine treatment with caution and increase blood test frequency to twice per week until blood results return to "green".
	Red	WCC < 3·0 and/or ANC < 1·5	WCC < 2·5 and/or ANC < 1·0	Stop clozapine treatment immediately. Conduct two blood tests over the next two consecutive days. If either test returns a "red" result, stop clozapine indefinitely, and register the person with the Central Non-Rechallenge Database.
US Food and Drug Administration (recommended criteria)	Normal range	ANC ≥ 1·5	ANC ≥ 1·0	The initial blood result must be in this range to start clozapine treatment. Then, continue clozapine treatment and blood monitoring, as per standard protocol.
	Mild neutropenia	ANC ≥ 1·0 and < 1·5	ANC ≥ 0·5 and < 1·0	Continue clozapine treatment and increase blood test frequency to three times per week until ANC returns to the normal range. For people with confirmed ADAN, initiate a haematology consultation.
	Moderate neutropenia	ANC ≥ 0·5 and < 1·0	*NA*	Stop clozapine treatment immediately and initiate haematology consultation. Perform daily blood tests until ANC ≥ 1·0, and then three times per week until ANC ≥ 1·5.
	Severe neutropenia	ANC < 0·5	ANC < 0·5	Stop clozapine treatment immediately and initiate haematology consultation. Do not rechallenge unless benefits outweigh risks. Perform daily blood tests until ANC ≥ 1·0 (for people with ADAN, ANC ≥ 0·5), and then three times per week until ANC ≥ 1·5 (for people with ADAN, ANC ≥ 1·0 or normal baseline value). If rechallenged, resume treatment as a new patient only when ANC reaches the normal range.

Evidence-based rationale for offering *ACKR1* genetic testing to people taking clozapine

We review the literature, split into four parts. Each section reviews a relevant area to evaluate the clinical need and rationale for offering *ACKR1* genetic testing to people taking clozapine. Our search strategy and selection criteria are described at the end of the manuscript. Key findings and statistics are summarised in Table 2.

ADAN diagnoses are missed or delayed in people taking clozapine

In the UK and elsewhere, ADAN is diagnosed by a haematologist.[21,30] People taking clozapine who present with low neutrophil counts should be reviewed, and diagnoses are confirmed when other potential causes of neutropenia have been excluded.[21,30] Consequently, ADAN diagnoses are currently made reactively after clozapine treatment has started. We review the evidence to understand whether ADAN diagnoses are missed or delayed, resulting in unnecessary exclusion from clozapine.

Several studies have assessed people with African ancestry (including those identifying as Black, African Caribbean, or African American), as ADAN and the Duffy-null genotype are more common in these groups.[26,37,39] People with African ancestry are more likely to have clozapine withdrawn due to neutropenia, but they are not more likely to develop agranulocytosis, suggesting ADAN diagnoses are potentially missed.[50,51] Studies of UK mental health services have found that the number of Black people taking clozapine with confirmed ADAN is lower than expected (8·4%[40] and 17%[21]), given that ~80% are predicted to carry the Duffy-null genotype.[37,39] Similarly, in a study of 552 people with African ancestry who were taking clozapine, just 14% had a diagnosis of ADAN, while 78% had the causal genotype.[34] Moreover, in a recent analysis of a London-based mental health trust, 39 out of 50 (78%) Black people taking clozapine were confirmed to have ADAN; however, 24 received their diagnosis only after *ACKR1* genetic testing.[42]

Three countries operate systems that actively prohibit clozapine rechallenge for people who develop neutropenia during treatment.[20] An example is the UK's Central Non-Rechallenge Database.[22] Registration should be reserved for people at risk of clozapine-induced agranulocytosis, as registrants are indefinitely prevented from clozapine rechallenge except when prescribed off-label.[22] A study of two UK-based mental health trusts found that 44% of Black people in the database had undiagnosed ADAN after re-assessment by a haematologist.[21] A retrospective analysis found that these people would not have been registered in the database had they been monitored with reduced ADAN thresholds at the beginning of their treatment.[21] A further study of a mental health trust in London identified 18 people in the database with undiagnosed ADAN, and 16 were successfully rechallenged with clozapine under haematology guidance, while 2 continued to record below-threshold blood results.[22] These studies highlight examples of unnecessary clozapine discontinuation, and the benefits of early (and pre-emptive) diagnosis.

There is also evidence that ADAN diagnoses are delayed. Studies have found that most diagnoses are confirmed following a below-threshold blood result or at clozapine

rechallenge (68%[21] and 88%[43]), rather than at the beginning of (or prior to) treatment. The time to obtain a diagnosis is also delayed, with the average ranging from 7 months[41] to 8·8 years.[22] The consequences of a delayed diagnosis are wide-ranging, especially for people diagnosed after clozapine discontinuation.[21,22,41] In a Canadian cohort of 41 people taking clozapine, 1,364 below-threshold blood results were recorded before diagnosis, requiring increased blood monitoring or interruption of treatment, while just 16 were recorded after ADAN was confirmed and revised thresholds were applied.[43] Moreover, increased blood monitoring and treatment disruption can lead people to seek alternatives to clozapine, often resulting in poorly controlled symptoms and lower quality of life.[40]

We conclude that there is clear evidence showing ADAN diagnoses are missed or delayed, resulting in unnecessary exclusion from clozapine.

Clozapine discontinuation often leads to adverse outcomes

While clinicians rapidly switch to another antipsychotic medication when neutropenia occurs, clozapine is the optimal therapy, and discontinuation should be reserved for people who cannot safely receive the treatment. We review the consequences of clozapine discontinuation.

Studies show that clozapine therapy is linked to positive outcomes for people who are treatment-resistant, including improved clinical response[9-11] and a significant reduction in all-cause mortality,[52,53] hospitalisation,[45,54] and risk of suicide.[46] A systematic review of 28 studies found that clozapine discontinuation is strongly linked to a worsening of psychiatric symptoms.[44] Studies included in the review found that hospital admissions occur less frequently in people taking clozapine, and people rechallenged with clozapine generally experience improved clinical outcomes.[44]

Studies have also assessed the damaging effects of abrupt clozapine discontinuation, which occurs when treatment is immediately stopped due to neutropenia. This can lead to a drug withdrawal syndrome, characterised by a rapid reappearance of psychosis symptoms, as well as vomiting, confusion, and stupor.[55] A meta-analysis found that "withdrawal-associated psychosis" occurs in 20·1% of clozapine-discontinuation cases,[56] and studies show that withdrawal occurs more frequently after abrupt, rather than gradual, discontinuation.[57-59]

Abrupt clozapine discontinuation can also have personal consequences, and these have been recorded in interviews with people taking clozapine in the UK.[60] They describe sudden discontinuation (due to neutropenia) as a traumatic experience that can jeopardise recovery and lead to hospitalisation.[60] It is important that revised monitoring thresholds are applied for people with ADAN so that unnecessary discontinuation is avoided.

***ACKR1* is the causal gene for ADAN**

A study including 6,005 people with African American ancestry first identified a T>C variant in *ACKR1* (single nucleotide polymorphism, rs2814778) to be strongly associated with low neutrophil counts.[31] This is the Duffy-null variant, and people homozygous for the variant, the Duffy-null genotype, were more likely to have low neutrophil counts than those carrying a copy of the functional allele.[31] The authors did not identify any other variants significantly associated with low neutrophil counts, suggesting the Duffy-null variant was the cause.[31]

Subsequent genome-wide analyses of 7,477[32] and 1,997[33] people with African American ancestry confirmed that the Duffy-null variant is strongly associated with low neutrophil counts (P = 1·0 × 10^{-237} and 4·09 × 10^{-53}, respectively), with no other significant associations being identified. The latter study, which compared people with low or high white blood cell counts (as a proxy for neutrophil counts), found that 36·8% with high counts also carried the Duffy-null genotype.[33] This highlights that not all people with the Duffy-null genotype present with (at least, at specific time points) low neutrophil counts, even though their genotype makes them more prone to do so.

A further genome-wide analysis was performed in 552 people with African ancestry receiving clozapine.[34] Consistent with previous findings, the Duffy-null variant was strongly associated with low neutrophil counts (P = 4·21 × 10^{-21}). During the study, 83 people with the Duffy-null genotype developed neutropenia resulting in immediate clozapine discontinuation, compared with two who carried a copy of the functional allele. Moreover, 97·3% of people with confirmed ADAN (diagnosed by a haematologist) carried the Duffy-null genotype, while 82·8% of people with the genotype remained undiagnosed.

Other studies have found that the Duffy-null variant is associated with low neutrophil counts in Yemenite Jews[61] and Latino populations.[62] In the latter study, the Duffy-null variant produced the strongest genome-wide signal for white blood cell counts (P = 5·68 × 10^{-56}) and neutrophil counts (P = 5·72 × 10^{-65}). In a further study of Brazilian people, *ACKR1* genetic testing was able to identify ADAN much more accurately than self-reported ethnicity (sensitivity = 97·4% vs 65·7%; specificity = 95·7% vs 48·8%).[63] Moreover, an analysis of UK Biobank and iPSYCH data found that people with the Duffy-null genotype had significantly lower neutrophil counts than those carrying the functional allele, regardless of self-reported ethnicity.[27] These findings support previous suggestions that the Duffy-null variant is more strongly associated with low neutrophil counts than ancestry,[31] and provide evidence that the variant produces the same phenotype in different populations globally.

These studies provide robust evidence that *ACKR1* is the causal gene for ADAN. This was acknowledged in the 2023 "European Guidelines on Diagnosis and Management of Neutropenia in Adults and Children",[30] which recommended that "benign ethnic neutropenia" be renamed to include *ACKR1* (and the alternative gene symbol, *DARC*) in the condition title, *ACKR1*/*DARC*-associated neutropenia.

People with the Duffy-null genotype can safely receive clozapine

We review the studies that have assessed *ACKR1* genetic testing alongside clozapine therapy. These are limited as *ACKR1* genetic testing is not routinely offered to people taking clozapine. For example, in the UK, the test can only be ordered locally by some specialised haematology departments.

A genome-wide association study assessed 552 people with African ancestry receiving clozapine in the UK.[34] This cross-sectional study included 83 people with the Duffy-null genotype who developed a below-threshold neutrophil count, which resulted in immediate clozapine discontinuation. 80 of these were rechallenged with clozapine, and 75 safely remained on treatment at the point of data collection (four discontinued treatment, and one died of a cause unrelated to neutrophil levels). Additionally, one person with the Duffy-null genotype had clozapine discontinued after developing a neutrophil count of $0{\cdot}4 \times 10^9$/L at week 15 of treatment (0·24% of participants with the Duffy-null genotype), but they were successfully rechallenged three days later with no further agranulocytosis reported during the study time period.

A six-month clinical trial assessed neutrophil counts in 274 people with African ancestry receiving clozapine at three sites in the USA and Nigeria.[64] 249 participants were genotyped, and 199 carried the Duffy-null genotype. Neutrophil counts were significantly lower in people with the Duffy-null genotype, and they had an eight-fold increased risk of neutropenia ($<1{\cdot}5 \times 10^9$/L, which is a UK "red" result). Throughout the study, just one person with the Duffy-null genotype developed agranulocytosis ($<0{\cdot}5 \times 10^9$/L). This is 0·36% of the study sample, which is similar to the expected rate of clozapine-induced agranulocytosis (0·4%).[18] It was also found that neutropenia occurred at least once in 27·4% of people with the Duffy-null genotype during six months of clozapine treatment. These results were transient, and discontinuation was not required. In the UK, a person without confirmed ADAN would have clozapine discontinued in a similar situation (if a consecutive test showed the same result).

These studies suggest that people with the Duffy-null genotype can safely receive clozapine without increased risk of agranulocytosis; however, they are more likely to have low neutrophil counts. This is unsurprising as the Duffy-null genotype is causal for ADAN, which is not associated with increased risk of agranulocytosis during clozapine treatment.[21,50,51,65] The challenge is that many people do not receive a diagnosis of ADAN and are at risk of treatment exclusion and discontinuation.

Summary of the evidence

Our review provides a clear justification for offering *ACKR1* genetic testing to people taking clozapine. There is evidence that ADAN diagnoses are missed or delayed, resulting in reduced access to clozapine and unnecessary discontinuation. We conclude that *ACKR1* genetic testing is a quick and accurate method for identifying people who are likely to have ADAN, offering added value over existing clinical procedures which are slow and ineffective. Moreover, our position is supported by other groups that have previously called for *ACKR1* genetic testing to help diagnose ADAN, including the UK's Royal College of Psychiatrists,[47] the Maudsley Prescribing Guidelines for Psychiatry,[48] the 2023 European Guidelines for Neutropenia,[30] and the Clozapine Handbook.[66]

In the next section, informed by expert opinion, we propose how *ACKR1* genetic testing could be offered in clinical practice to people taking clozapine.

***Table 2*. Summary of supporting evidence for offering *ACKR1* genetic testing to people taking clozapine.**

	Author, year	Study design	Sample size (*n*)	Sample description	Sample demographic	Study aim	Key findings
Evidence showing ADAN diagnoses are missed or delayed	Aziri H *et al*, 2024[42]	Observational study	108	People taking clozapine	Black (46·3%), White (35·2%), Asian (4·6%), Mixed (4·6%), Other (9·3%)	To assess prevalence of ADAN in people taking clozapine	26 of 108 people taking clozapine (24%) were found to have ADAN and the Duffy-null genotype after *ACKR1* genetic testing. 24 of the 26 people self-identified as Black.
	Wu S *et al*, 2024[43]	Retrospective chart review	41	People taking clozapine	African Caribbean (49%), African (34%), African North American (12%), Middle Eastern (2%), and Indian Caribbean (2%)	To evaluate the safety of clozapine treatment in people with ADAN	ADAN was diagnosed mostly after a below-threshold blood result (83%), followed by clozapine initiation (12%) and clozapine rechallenge (5%). 1,364 below-threshold blood results were recorded before ADAN diagnosis, compared to 16 after diagnosis.
	Oloyede E *et al*, 2022[41]	Modelling study	3,731	People registered with the UK CNRD	White (83%), Black (10%), Asian (5%), and Other (2%)	To examine implications of revising UK clozapine monitoring guidelines	The median time to ADAN diagnosis from clozapine initiation was 7 months (IQR 0 – 34).
	Oloyede E *et al*, 2021[22]	Retrospective observational study	115	People registered with the UK CNRD	White (47%), Black (39%), Asian (8%), and Other (6%)	To examine implications of revising UK clozapine monitoring guidelines	The mean time to ADAN diagnosis from clozapine initiation was 8.8 years (SD ± 8.1). 18 people in the UK CNRD had undiagnosed ADAN, and 16 were successfully rechallenged with clozapine.
	Oloyede E *et al*, 2021[21]	Retrospective observational study	2,020	People taking clozapine	Non-Black (72%), Black (28%)	To evaluate the extent of undiagnosed ADAN in the UK CNRD	ADAN was diagnosed mostly after a below-threshold result or at clozapine rechallenge (68%), compared with clozapine initiation (32%). Of 574 Black people, 17% had a formal diagnosis of ADAN (provided by a haematologist), and 8 of 18 (44%) Black people in the UK CNRD were diagnosed with ADAN after haematologist re-assessment.
	Legge SE *et al*, 2019[34]	Genome-wide association study	552	People taking clozapine	African (100%)	To identify risk alleles for low neutrophil levels in people taking clozapine	14% of people with African ancestry were diagnosed with ADAN, while 78% carried the causal Duffy-null genotype.
	Whiskey E *et al*, 2011[40]	Retrospective observational study; case series	195 (including 4 individual case studies)	People taking clozapine	Black (49·7%), White (38·7%), Mixed race (4·7%), Asian (4·2%), and Other (2·6%)	To study ADAN diagnoses in Black people, and the real-life consequences of a missed diagnosis	Of 95 Black people receiving clozapine in a London hospital, only 8 (8·4%) were registered with ADAN, while ~80% would be predicted to have the causal Duffy-null genotype.[37,39]
Evidence showing adverse outcomes linked to clozapine discontinuation	Oloyede E *et al*, 2023[60]	Qualitative cross-sectional study	8	People taking clozapine, and their carers	*NA*	To explore perspectives about clozapine discontinuation in people taking clozapine and their carers	Two main themes were identified: (1) The threat of a below-threshold blood result and the associated risk of clozapine discontinuation can be a traumatic experience; (2) The priorities of people taking clozapine include staying in the community (and not being admitted to hospital) and having contingency plans for when clozapine is discontinued.
	Miura G *et al*, 2022[44]	Systematic review	28 studies	*NA*	*NA*	To determine clinical outcomes following clozapine discontinuation	Main findings included: (1) Psychiatric symptoms worsen after clozapine discontinuation; (2) People generally respond well after clozapine rechallenge; (3) People generally respond poorly to other antipsychotic drugs after clozapine discontinuation.
	Moncrieff J, 2006[56]	Meta-analysis	10 studies	*NA*	*NA*	To assess evidence for withdrawal-associated psychosis	Withdrawal-associated psychosis occurs in 20·1% of cases (95% CI = 14.9 – 25.3) following clozapine discontinuation.

Evidence showing ACKR1 is the causal gene for ADAN	Legge SE *et al*, 2020[27]	Retrospective observational study	7,925 and 281	Participants from UK Biobank and iPSYCH	Black African/Caribbean (100%)	To investigate the association between the Duffy-null genotype and infection rates	The Duffy-null genotype was significantly associated with lower ANC levels in Black African/Caribbean people (P = 3·52 × 10^{-293}) and those with other ancestries (P = 4·41 × 10^{-129}).
	Legge SE *et al*, 2019[34]	Genome-wide association study	552	People taking clozapine	African (100%)	To identify risk alleles for low neutrophil levels in people taking clozapine	rs2814778 was significantly associated with low ANC during clozapine treatment (P = 4·21 × 10^{-21}). People homozygous for the C allele at rs2814778 (Duffy-null genotype) were significantly more likely to develop neutropenia and to have clozapine discontinued (P = 3·44 × 10^{-7}). 72 out of 74 people (97·3%) formally diagnosed with ADAN (by a haematologist) had the Duffy-null genotype.
	Charles BA *et al*, 2018[33]	Genome-wide association study	1,178	Participants from the REGARDS study	African American (100%)	To identify risk alleles for low neutrophil levels and ADAN	rs2814778 was significantly associated with low neutrophil counts in African American people with ADAN (P = 4·09 × 10^{-53}).
	Jain D *et al*, 2017[62]	Genome-wide association study	11,809	Participants from the HCHS/SOL study	Hispanic/Latino American (100%)	To identify risk alleles that contribute to WCC and immune cell subtype variability	rs2814778 was significantly associated with total WCC counts (P = 5·68 × 10^{-56}) and neutrophil counts (P = 5·72 × 10^{-65}).
	Dinardo CL *et al*, 2017[63]	Case control study	83	Brazilian sample with confirmed ADAN	Cases - White (34·3%), Black (21%), and Mixed (44·7%) Controls - White (48·9%), Black (8·9%), and Mixed (42·2%)	To evaluate accuracy of Duffy-null genotyping and self-declared ancestry for diagnosing ADAN	Duff-null genotyping (sensitivity 97·3%, specificity 95·6%, PPV 94·8%, NPV 94·7%) was more accurate than self-reported ethnicity (sensitivity 65·7%, specificity 48·8%, PPV 52%, NPV 62·8%) for diagnosing ADAN.
	Reiner AP *et al*, 2011[32]	Genome-wide association study	16,388	Participants from seven cohorts - ARIC, CARDIA, JHS, WHI, HANDLS, Health ABC, and GeneSTAR	African American (100%)	To identify risk alleles that contribute to WCC and immune cell subtype variability	rs2814778 was significantly associated with total WCC counts (P = 1·0 × 10^{-524}) and neutrophil counts (P = 1·0 × 10^{-237}).
	Reich D *et al*, 2009[31]	Analysis of genotype and phenotype data	6,005	Participants from three cohorts - ARIC, JHS, and Health ABC	African American (81·8%) and European (18·2%)	To identify risk alleles for low WCC in African American people	rs2814778 was the only significant locus predictive of WCC and neutrophil count in African American people (P = 3·8 × 10^{-5}).
Evidence showing that people with the Duffy-null genotype can safely receive clozapine	Kelly DL *et al*, 2023[64]	Open-label clinical trial	227	People taking clozapine	Black (93·1%), White (2·2%), Native American (0·4%), Asian (0·4%), and Other (4%)	To assess ANC variability and clozapine safety in people with African ancestry	The Duffy-null genotype was associated with an eight-fold increased risk of developing neutropenia (P = 0·0014). Across 1,467·6 person-months of clozapine exposure, severe neutropenia was observed in just one participant (0·36%). In people who developed neutropenia, 96·5 % (65 out of 68 participants) had the Duffy-null genotype.
	Legge SE *et al*, 2019[34]	Genome-wide association study	552	People taking clozapine	African (100%)	To identify risk alleles for low neutrophil levels in people taking clozapine	Among people with the Duffy-null genotype with an ANC <1·5 × 10^9/L, 94% (75 out of 80) were successfully rechallenged with clozapine (four discontinued treatment, one died of a cause unrelated to neutrophil levels). One person with the Duffy-null genotype presented with an ANC of 0·4 × 10^9/L (0·24%) but were successfully rechallenged three days later with no further agranulocytosis results.

ADAN = *ACKR1*/*DARC*-associated neutropenia; ANC = absolute neutrophil count; CI = confidence interval; CNRD = Central Non-Rechallenge Database; IQR = interquartile range; NA = not applicable; NPV = negative predictive value; PPV = positive predictive value; WCC = white cell count.

Expert-led proposal

We are a diverse multi-disciplinary team of psychiatrists, haematologists, pharmacists, pharmacologists, geneticists, clinical scientists, health economists, and lived experience representatives from a patient and carer group. Together, we propose a new and forward-thinking framework for how to offer *ACKR1* genetic testing to people taking clozapine. Our aim is to provide guidance that facilitates prompt, unobstructed, and equitable access to clozapine, which can be integrated with existing clinical pathways and safety measures. This proposal is intended to be internationally relevant and should be generalisable across countries, including those that recommend different monitoring criteria for people taking clozapine.[4,20]

This proposal focuses on people taking clozapine for treatment-resistant schizophrenia, although it is equally applicable for other clozapine indications. In the UK and elsewhere, clozapine is also recommended as a second-line treatment for persistent psychosis in Parkinson's disease, after a failed trial of quetiapine.[1,67,68] However, clozapine is underused for this indication,[67,68] and the vast majority of clozapine prescriptions are for people with treatment-resistant schizophrenia.

Test eligibility criteria

Clozapine monitoring guidelines vary widely between countries (Appendix 1).[20] We propose eligibility criteria for *ACKR1* genetic testing that may be applied internationally within existing monitoring protocols, and that facilitate equitable access to clozapine. It is not necessary or feasible – logistically or financially – to offer *ACKR1* genetic testing to all people taking clozapine. A meta-analysis of 108 studies pooling 119,592 participants showed that the peak incidence of clozapine-induced agranulocytosis occurs at one month of treatment and declines to negligible levels after one year.[18] However, we note from clinical experience that some people with the Duffy-null genotype can develop neutropenia later in treatment, having initially presented with normal neutrophil counts, and we consider this below.

In Box 1, we recommend three eligibility criteria that are appropriate for adults, young people, and children.

***Box 1*. Proposed eligibility criteria for an *ACKR1* genetic test**

Criterion 1: Pre-emptive testing for all people who are due to start clozapine

We recommend that all people who are due to start clozapine should be offered pre-emptive *ACKR1* genetic testing, regardless of their ethnicity. This will ensure that reduced thresholds for ADAN can be applied promptly, minimising treatment disruption and delay.

Self-reported ethnicity is an unreliable measure of genetic ancestry.[69,70] Studies show that any person can have the Duffy-null genotype, irrespective of whether they self-report African or Middle Eastern ethnicity.[27,31,39,63] Testing solely on the basis of self-reported ethnicity would result in ADAN diagnoses being missed.

At present, the *ACKR1* genetic test can take between one and four weeks to return a result. Therefore, a pre-emptive testing approach offers the best opportunity to identify all people with the Duffy-null genotype in a timely manner that effectively prevents unnecessary clozapine discontinuation or disruption.

Criterion 2: Reactive testing for people taking clozapine who register a neutrophil count below the normal range

People who return a neutrophil count below the normal range are at imminent risk of abrupt clozapine discontinuation. We recommend offering a reactive *ACKR1* genetic test to all people who meet this criterion, unless already tested. The neutrophil count thresholds for this criterion should be those recommended by each country's clozapine monitoring system.

Criterion 3: Testing for people who have had clozapine discontinued due to neutropenia

Studies have identified people with undiagnosed ADAN in the UK's Central Non-Rechallenge Database.[21,22] Outside the UK, most countries do not operate a non-rechallenge database, whereby a manufacturer off-licence agreement is required to rechallenge with clozapine.[20] However, an international analysis in 2022 found that 41 countries also prohibited clozapine rechallenge after suspected agranulocytosis.[20] In these situations, people with the Duffy-null genotype may have clozapine discontinued unnecessarily and may be prevented from vital clozapine therapy.

To address this, we recommend that healthcare services and prescribers should consider *ACKR1* genetic testing for people who have had clozapine discontinued due to neutropenia. New information about *ACKR1* status may help prescribers to decide whether to rechallenge with clozapine, and to determine the cause of a person's low neutrophil counts.

[End of Box 1]

Strategies for implementing *ACKR1* genetic testing in different settings

We recommend pre-emptive *ACKR1* genetic testing for all people starting clozapine (criterion 1). Due to the variable nature of neutrophil counts, people with the Duffy-null genotype may initially present with a neutrophil count in the normal range.[27,64] These people may be missed by reactive testing and may experience unnecessary disruption or discontinuation of clozapine. Therefore, criterion 1 is the optimal strategy to facilitate equitable access to clozapine for people with the Duffy-null genotype.

However, we recognise that pre-emptive testing may not be feasible in some places due to limited resources or testing capacity. In these situations, criterion 1 could be omitted and a reactive testing approach based purely on a neutrophil count threshold (criterion 2) could be considered. This approach will still identify many people with the Duffy-null genotype while reducing the overall number of tests conducted. Under criterion 2, *ACKR1* genetic testing should be offered to all people presenting with a neutrophil count

(and if applicable, white cell count) that is below the normal range, based on the thresholds recommended by each country's clozapine monitoring system (examples in Table 1 and Appendix 1).

We consider the three eligibility criteria to be complementary. Depending on the circumstances of a healthcare setting, the criteria may be implemented in stages and different orders.

Integrating *ACKR1* genetic testing into clinical practice

We recommend that clozapine prescribers – usually (but not always) psychiatrists – should interpret *ACKR1* test results and promptly apply revised thresholds for people with the Duffy-null genotype without haematology input or sign-off. As the Duffy-null genotype is causal for ADAN,[27,31-34,62,63] we suggest there is robust evidence supporting this approach. This will ensure that revised thresholds are applied as soon as possible, including in places with limited access to haematology support. If haematologists are required to confirm ADAN before revised thresholds can be applied, then some areas will experience lengthy delays and treatment disruption. For these people, the benefits of *ACKR1* genetic testing will not be realised.

To ensure safe access to clozapine, we suggest that people with the Duffy-null genotype who have neutropenia under the revised ADAN thresholds should be assessed remotely by a haematologist. This will ensure that all neutropenia cases are investigated.

Additionally, we recommend that people who do *not* have the Duffy-null genotype but who have neutropenia, either in isolation or as part of a more general full blood count abnormality, should be assessed according to a country's standard protocol for neutropenia management.

We are aware that most countries do not recommend specific neutrophil count thresholds for people with ADAN / the Duffy-null genotype.[20] In these situations, revised thresholds that are lower than the country's standard thresholds should be considered by the relevant regulatory body. Examples of established monitoring thresholds for ADAN in the UK and USA are shown in Table 1 and have been reviewed previously.[20]

This is a prescriber-led approach that aims for prompt and equitable access to clozapine for people with ADAN, while prioritising people with neutropenia for remote haematology review. We suggest that this approach is generalisable across countries.

We describe the actions needed to integrate *ACKR1* genetic testing into clinical practice in Box 2 and a flow diagram in Figure 1.

***Box 2*. Actions for integrating *ACKR1* genetic testing into clinical practice**

Requesting the test

The prescriber should explain the reason for testing and seek consent from the person eligible for the test. Subsequently, the test sample may be obtained during the baseline or any routine blood tests. The standard clozapine monitoring and treatment pathway

should not be altered or delayed while waiting for the genetic test result (i.e. if appropriate, clozapine should be started without delay).

Actions when ACKR1 homozygous variant is detected

If the *ACKR1* homozygous variant is detected (Duffy-null genotype, C/C at rs2814778), the result should be recorded in the person's health record (and if applicable, with their clozapine monitoring registry) using commonly used medical term coding (i.e. SNOMED CT ID for Duffy-null phenotype; ICD-11 code for benign ethnic neutropenia). The prescriber should apply revised (i.e. reduced) blood monitoring thresholds for ADAN, which may differ depending on country of practice.

If the person presents with neutropenia at any point (i.e. a neutrophil count below the normal range having applied the revised ADAN threshold), the prescriber should initiate a remote consultation with a haematologist to determine the cause. We suggest that an in-person consultation is not required, and the assessment can be made by remotely evaluating a person's blood results and clinical records. This is supported by European guidelines that suggest extensive work-up is not required for people confirmed to have the Duffy-null genotype.[30]

The prescriber should not wait for the haematology opinion. Clozapine should be started, continued, stopped, or withheld according to protocol and under revised thresholds for ADAN. When the haematology opinion is returned, the cause of neutropenia should be recorded in the person's health record and acted upon if necessary.

If the person does not have neutropenia, neutrophil counts should continue to be monitored using revised ADAN thresholds and according to protocol.

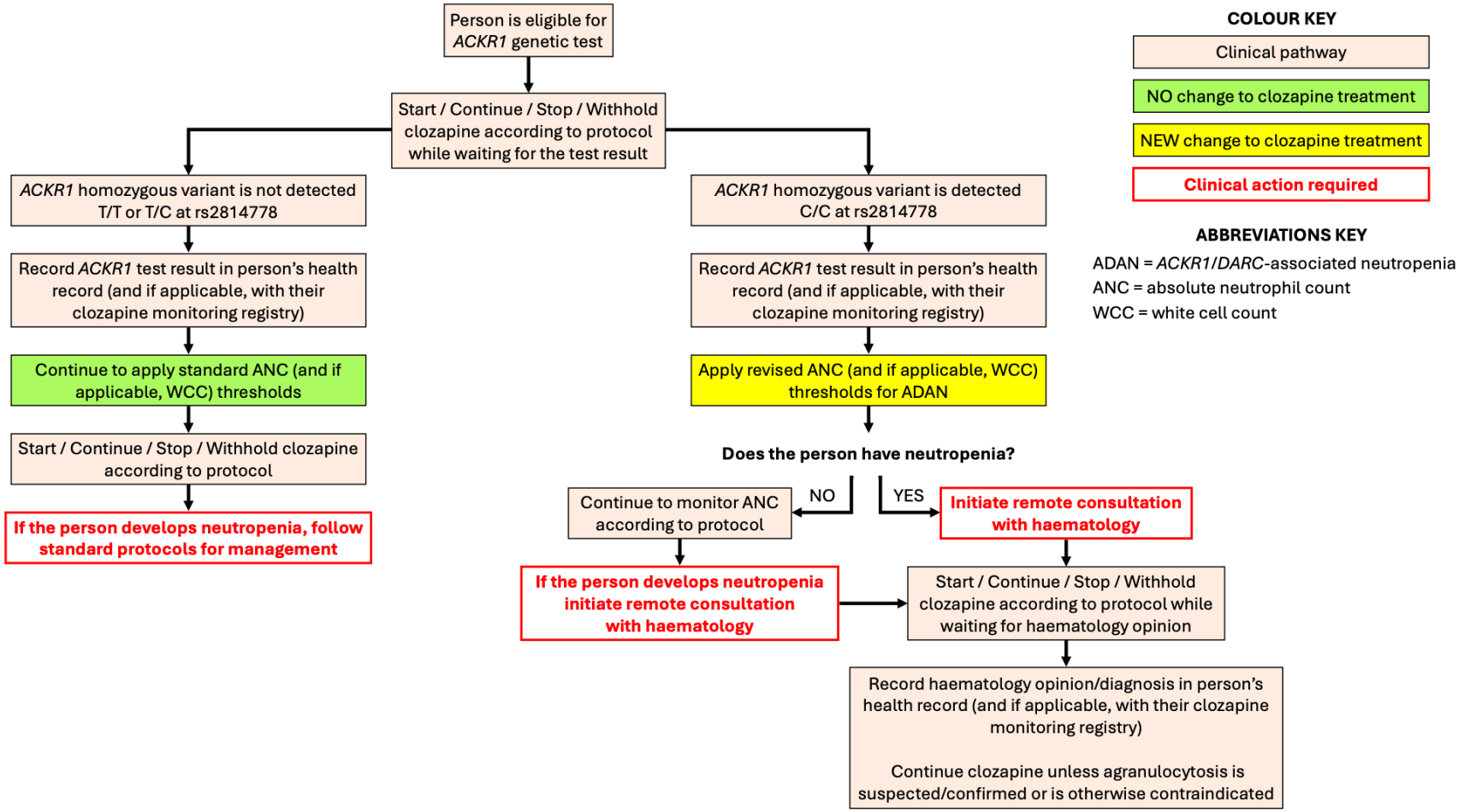
Actions when ACKR1 homozygous variant is not detected

If the *ACKR1* homozygous variant is not detected (T/T or T/C at rs2814778), the result should be recorded in the person's health record (and if applicable, with their clozapine monitoring registry) using commonly used medical term coding (i.e. SNOMED CT ID for the person's Duffy blood group phenotype). For people due to start or already taking clozapine, standard blood monitoring thresholds should continue to be applied. For people who have neutropenia, standard protocols for management should be followed.

[End of Box 2]

***Figure 1*. Flow diagram showing how *ACKR1* genetic testing could be integrated into clinical practice [NEW FIGURE ADDED]**

Colour and abbreviations keys are shown. Light orange / beige boxes describe the clinical pathway; the green box describes no change to clozapine treatment; the yellow box describes a new change to clozapine treatment; boxes with a red border and text describe where clinical action is required. ADAN = *ACKR1*/*DARC*-associated neutropenia; ANC = absolute neutrophil count; WCC = white cell count.



Health economic analysis

Hospitalisation costs are 60-fold higher for people with treatment-resistant schizophrenia, compared with the general US population.[8] Clozapine is an effective treatment that can reduce the number and duration of hospital admissions, which can substantially lower healthcare costs.[45,71-74] Community-initiated clozapine treatment also produces cost savings by reducing outpatient visits and pressures on other services.[75] Given that clozapine is a cost-effective treatment, increasing access to clozapine through *ACKR1* genetic testing is potentially a cost-effective intervention.

We performed a cost analysis for the three eligibility criteria (Box 1) to estimate the costs from the first year of *ACKR1* genetic testing for the UK as a representative national healthcare system. Results are shown in Table 3 and full calculations (including formulas for reproducibility) are shown in Appendix 2.

For criterion 1, to estimate the number of people who will start clozapine treatment each year, we used a UK population estimate for 16–64 year olds of 43,295,000 people;[76] an annual schizophrenia incidence rate for people aged 16–64 in England of 15·2 per 100,000 person-years, which we assumed was generalisable for the UK;[77] and we assumed 30% would be treatment resistant.[7] This gave an estimated 1,974 people per year eligible under criterion 1 (Table 3). This number should remain constant in subsequent years of testing.

For criterion 2, we assumed that neutropenia occurs in 3·8% of people taking clozapine.[18] This value was generated from a meta-analysis that defined neutropenia as counts <1·5 × 10^9/L.[18] We also used the number of people estimated to start clozapine treatment each year in the UK (1,974), rather than the total number of people taking clozapine, as 89% of neutropenia cases occur during the first 12 months of treatment.[18] Consequently, this gave a conservative estimate of 75 people eligible in the first year of testing (Table 3).

For criterion 3, we used data from the UK's Central Non-Rechallenge Database.[41] We assumed that people recently registered in the database would be more likely to be tested than those registered several years ago. Consequently, we estimated the number of database registrations within the past three years, which gave 588 people eligible in the first year of testing (Table 3).[41]

If criterion 1 is applied, the number of tests under criteria 2 and 3 may decrease in subsequent years as people are tested pre-emptively at the beginning of treatment. Therefore, cost savings estimates provided here are for the first year of testing.

We then estimated the number of tested people who would be expected to have the Duffy-null genotype. For criteria 1 and 2, we used UK Census 2021 ethnicity data,[78-80] as people with African and Middle Eastern ancestry are more likely to have the Duffy-null genotype.[37,39] While necessary for calculating estimates of the number of people who have the Duffy-null genotype (in the absence of real-world data since *ACKR1* testing is not routinely available), we stress that self-reported ethnicity is not a suitable measure for selecting people for *ACKR1* testing in clinical practice. This is due to limited accuracy

of self-reported ethnicity as well as ethical concerns.[69,70] Regarding ethnicity data, the censuses for England and Wales, Scotland, and Northern Ireland are managed independently.[78-80] Therefore, we obtained data per member country for the percentage of people with Black, African, and/or Caribbean ethnicity (between 0·58% and 4%) and Arab ethnicity (between 0·1% and 0·6%), which we used to capture people with Middle Eastern ancestry.[78-80] For criterion 3, we assumed that 9·6% of people registered with the Central Non-Rechallenge Database would have Black, African, and/or Caribbean ethnicity based on pre-existing data, which reflects their overrepresentation in the database.[41] We used Duffy-null variant frequencies (for African and Middle Eastern ancestry, as well as European ancestry to represent the majority of the remaining test population in the UK)[39] to calculate detection rates (also known as the test yield, which is the percentage of tested people who return the Duffy-null genotype) of 3·85% (criteria 1 and 2) and 8·54% (criterion 3).[41] We suggest that these values are cautious and likely to be underestimates, not least because we did not include people with mixed ancestry or people with Middle Eastern ancestry, as these are not clearly defined in the UK Census 2021.[78-80]

To calculate cost impacts, we used prices of £60 per test based on a similar assay for single nucleotide variants in the *DPYD* gene, which is nationally available in the UK (Skowronska, personal communication 2025), and £169 per test based on a targeted sequencing test for the Duffy-null variant which is provided by a non-routine local service in London (Smith and Rees, personal communication 2025). We have not included the cost of the prescriber's time for ordering and interpreting the test, but this cost would be small and captured within the test price range that we have considered. Additionally, there is uncertainty surrounding the annual cost saving per patient associated with clozapine to the UK healthcare system. Estimates range from £3,783, calculated from a study comparing prompt provision of clozapine versus a delay of 3·98 years,[81] to another study reporting per person annual savings of £6,864, based on a reduction in hospitalisation costs.[72] For this reason, our analysis presents conservative estimates (lower clozapine saving value and higher genetic test cost) and anti-conservative estimates (higher clozapine saving value and lower genetic test cost).

Our conservative estimates range from a net annual incurred cost of £46,108 (criterion 1) to a cost saving of £90,592 (criterion 3), while our anti-conservative estimates include cost savings from £15,324 (criterion 2) to £403,269 (criterion 1). In the first year of genetic testing, including all criteria together, estimates of the total cost saving for the UK healthcare system range from £42,732 (conservative) to £727,990 (anti-conservative) (Table 3). *ACKR1* genetic testing is required once in a lifetime; therefore, in subsequent years, cost savings associated with clozapine therapy would continue to accrue, while the number of people needing the genetic test would reduce over time.

For year one, we estimate 129 people with the Duffy-null genotype would be identified and would receive clozapine, having conducted 2,637 tests. This gives a number needed to test value of 20 (Appendix 2). Based on a whole-disease model of UK services for schizophrenia, and compared with using other antipsychotic drugs, these people would each experience a discounted, lifetime increase in quality-adjusted life years (QALYs) of 0·0086 per person (or 1·11 QALYs across all 129 people).[74] From year two, we assumed

that criterion 3 may not be applied as people are likely to be tested in year one. Therefore, considering criteria 1 and 2 only, we estimate a number needed to test value of 26 from year two onward (Appendix 2).

Finally, we have considered the current cost range of a single *ACKR1* genetic test. In future, genetic testing costs are likely to reduce as demand increases and technologies become widely available. In particular, the Duffy-null variant could be included in a multi-gene panel (i.e. a pharmacogenetics gene panel), whereby a person would need to be tested once for multiple genetic variants to benefit from pharmacogenetics-informed treatments across the remainder of their lifetime. We anticipate that multi-gene panel approaches will enhance cost savings for healthcare systems.

***Table 3*. Estimated test numbers and cost savings across the UK in the first year of *ACKR1* genetic testing**

Footnotes are described beneath the table. Cell values were rounded to the nearest integer.

	Estimates for the UK population per year			
	Eligible people	**Expected people with Duffy-null genotype**	**Cost of testing** [a] conservative (anti-conservative)	**Cost savings** [b] conservative (anti-conservative)
Criterion 1: Pre-emptive testing for all people who are due to start clozapine	1,974 [c]	76 [d]	£333,649 (£118,455)	-£46,108 (£403,269)
Criterion 2: Reactive testing for people taking clozapine who register a neutrophil count below the normal range	75 [c,e]	3 [d]	£12,679 (£4,501)	-£1,752 (£15,324)
Criterion 3: Testing for people who have had clozapine discontinued due to neutropenia	588 [f]	50 [g]	£99,372 (£35,280)	£90,592 (£309,397)
TOTAL	2,637	129	£445,699 (£158,236)	£42,732 (£727,990)

[a] Using £169 (conservative) and £60 (anti-conservative) as cost per *ACKR1* genetic test
[b] Using annual cost saving of £3,783 per person (conservative)[81] and £6,864 per person (anti-conservative);[72] both values were inflated to August 2025 value using the Bank of England inflation calculator;[82] to calculate cost savings, the cost of testing was deducted
[c] Using Labour Force Survey data for 16–64 year olds in May–July 2025,[76] schizophrenia incidence rate of 15·2 per 100,000 person-years,[77] assumption that 30% of people are treatment resistant[7]
[d] Using 3·85% detection rate for people with the Duffy-null genotype, calculated from UK Census ethnicity data[78-80] and Duffy-null variant frequencies[39]
[e] Assuming 3·8% of people taking clozapine develop neutropenia ($<1{\cdot}5 \times 10^9$/L)[18]
[f] Estimated registrations with the UK's Central Non-Rechallenge Database in the past three years[41]
[g] Using 8·54% detection rate for people with the Duffy-null genotype, accounting for overrepresentation of people with Black, African, and/or Caribbean ethnicity in the UK's Central Non-Rechallenge Database[41]

Conclusion

Mental health services are not currently equipped to identify ADAN in people taking clozapine. *ACKR1* genetic testing offers a fast and accurate solution, and we recommend that testing should be available for people taking clozapine. Our prescriber-led proposal will facilitate rapid identification of ADAN while preserving existing safety measures. Our proposed test criteria may be applied either in full or in part across different settings and countries, depending on available resources. Increasing access to clozapine will lead to better outcomes, as well as cost savings for healthcare systems. This proposal is a call to action. A simple genetic test will enable more people to safely receive a vitally important medication.

Search strategy and selection criteria

The literature search was conducted systematically using PubMed. Search strategies included key terms that were relevant for each subsection described in the evidence section. Terms with multiple names were included in the search strategy, such as “BEN” and “benign ethnic neutropenia”, alongside the newly accepted term, “ADAN”. No restrictions were applied to study type, geographical location, or language, although searches were made using English. Reference lists of papers were screened for other relevant literature.

Data availability statement

Underlying data for the health economic analysis (Table 3) were calculated from publicly available data or provided as personal communications. No other data were generated for this manuscript. All data and calculations are shown in Appendix 2.

Code availability statement

Full calculations and formulas for the health economic analysis are shown in Appendix 2.

Inclusion and ethics statement

This article and its recommendations are intended for an international audience.

Declaration of interests

Dyfrig A Hughes is Chair of the National Pharmacogenomics Group for NHS Wales, and co-chair of the Pharmacogenomics Test Evaluation Group for NHS England.

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Munir Pirmohamed is Advisory Board Chair for Bosch Health Foundation (Stuttgart, Germany), Vice Chair for Qatar Precision Health Initiative, Chair for Commission on Human Medicines, Medical Trustee for British Heart Foundation, Council Member for Medical Research Council, Chair for Prix Galien Foundation UK.

Elvira Bramon is a member of the Pharmacogenomics Test Evaluation Group for NHS England, and a member of the NHS England National Genomics Education Programme GeNotes Mental Health Working Group.

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All other authors declare no conflict of interest.

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APPENDIX 1

Clozapine Monitoring Across Different Countries (Adapted from Oloyede *et al*, 2022[1])

Country	Monitoring Requirement	ADAN Considerations	Discontinuation Criteria	Clozapine Rechallenge Restrictions	Source Type (Year)
Africa					
South Africa	Mandatory [A]	Not specified [B]	ANC < 1·0 x 10^9/L	Not specified	National Guideline (2024)[2]
Oceania					
Australia	Mandatory	Not specified	WCC < 3·0 x 10^9/L, ANC < 1·5 x 10^9/L	Rechallenge considered [C]	Regional Guidelines (2022, 2024)[3,4]
Asia					
Thailand	Recommended (not mandatory)	Not specified	Not specified	Not specified	National Guideline (2000)[5]
Europe					
Netherlands	Mandatory (but can be stopped at 6 months at patient request)	People with confirmed ADAN can be monitored under reduced WBC and ANC thresholds. No specific thresholds given [D]	WCC < 3·0 x 10^9/L, ANC < 1·5 x 10^9/L	Rechallenge considered [E]	Clozapine Plus Working Group guideline (2013)[6]
North America					
Canada	Mandatory	People with confirmed ADAN can be monitored under reduced ANC thresholds	ANC < 1·5 x 10^9/L (general), < 0·5 x 10^9/L (ADAN)	People given non-rechallenge status cannot resume clozapine	Summary of Product Characteristics (2025)[7]
South America					
Chile	Mandatory	ADAN mentioned with recommendation that if ANC ≥ 1·0 x 10^9/L, clozapine use is safe	ANC < 1.0 x 10^9/L (Same threshold applied for general population and ADAN)	ANC < 1·0 x 10^9/L is a relative contraindication; if ANC < 0·5 x 10^9/L, rechallenge can only be considered if benefits clearly outweigh risks	National Guideline (2018)[8]

ADAN = *ACKR1*/*DARC*-associated neutropenia; ANC = absolute neutrophil count; WCC = white cell count

[A] The South African *Standard Treatment Guidelines and Essential Medicine List (*STG/EML*)* (2024) uses language such as "check" and "monitor", which suggests that monitoring is a requirement for clozapine use. However, (to the best of our knowledge) unlike countries with national clozapine registries (such as the UK), South Africa does not maintain a centralised system to enforce monitoring, making the "*no blood, no drug*" rule unlikely to be present.

[B] ADAN (or benign ethnic neutropenia / BEN) is not mentioned in the published STG/EML. Previous documents from the *National Essential Medicines List Committee* (NEMLC) in 2017–2019 considered using lower ANC thresholds for people with ADAN (< 0·5 x 10^9/L).[9] Due to concerns about risk of infectious disease, lower thresholds were not included in the final guideline.

[C] Rechallenge can be considered after consultation with a haematologist and clear evidence that the cause of the low white cell count was not due to clozapine use.

[D] Oloyede *et al,*[1] suggest there are no adjusted ADAN thresholds in guidelines provided by the Netherlands, likely because specific values are not stated. We note that the guideline provided by the Clozapine Plus Working Group acknowledges ADAN and suggests lower thresholds, indicating its clinical recognition even without stated values.

[E] Rechallenge in the Netherlands requires haematology consultation and may only be considered if the WCC has not fallen below 2·0 x 10^9/L and there is clear evidence that the cause of the low white cell count was not due to clozapine use. Informed consent from the patient or a legal representative is also required.

Note, where there are minor discrepancies between this table and Table S2 from Oloyede et al,[1] *these may reflect differences in guideline editions, the level of publicly available information (available to the authors of this table at the time of writing), or differences between column headings. Countries were selected based on availability of published guidelines / documentation in English (except for the Chilean national guideline, for which a translation was provided).*

Brief Summary:

Clozapine monitoring guidelines differ substantially across countries. Monitoring is mandatory in South Africa, Australia, Canada, and the Netherlands (although in the Netherlands monitoring may be stopped after six months of treatment), while in Thailand monitoring is recommended but not mandatory. Global acknowledgement of ADAN also varies. Clozapine guidelines available in South Africa, Australia, and Thailand do not mention ADAN or provide adjusted thresholds. By contrast, the Summary of Product Characteristics used in the Netherlands recognises that people with ADAN may receive reduced thresholds, although specific thresholds are not stated. Canadian guidelines recommend that people with ADAN should receive reduced ANC thresholds. Discontinuation criteria also differ. Guidelines provided by Thailand do not state specific monitoring thresholds nor do they mention discontinuation criteria. Guidelines in South Africa recommend an ANC cut-off of $< 1{\cdot}0 \times 10^9$/L, while guidelines in Canada, Australia, and the Netherlands apply a $< 1{\cdot}5 \times 10^9$/L ANC discontinuation threshold. Clozapine rechallenge policies are also inconsistently described. Australia and the Netherlands permit rechallenge under specific conditions, while Canada recommends a strict non-rechallenge status for people who develop low white cell counts while taking clozapine. South Africa and Thailand do not provide guidance on clozapine rechallenge.

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