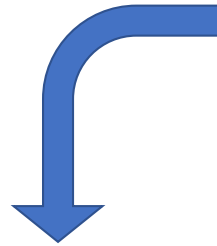


(A)

Current estimated proportion of CIAG and HLA-B*59:01

	HLA-B*59:01 (+)	HLA-B*59:01 (-)	total
CIAG	1,280	4,160	5,440
CIAG (-)	2,681	91,879	94,560
Total	3,961	96,039	100,000



	HLA-B*59:01 (+)	HLA-B*59:01 (-)	Sub total
CIA	396 (~30%)	692	1,088
CIG	884 (~70%)	3,468	4,352
Sub total	1,280 (100%)	4,160	5,440

set "CIAG prevention rate" = 0.3

$$1,280 \times 0.3 = 384$$

if we prevent CIG in subjects with HLA-B*59:01, a maximum ~70% CIAG prevention rate can be obtained.

Expected proportion by "HLA-guided treatment schedule"

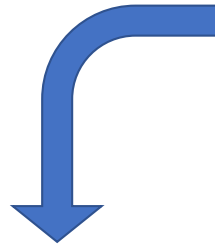
	HLA-B*59:01 (+)	HLA-B*59:01 (-)	Sub total'
CIA	396	692	1088
CIG	500	3,468	3,968
Sub total	896	4,160	5,056

(~7.0% reduction)

(B)

Current estimated proportion of CIAG and HLA-B 158T/HLA-DQB1 126Q

	HLA-B 158T/HLA-DQB1 126Q(+)	HLA-B 158T/HLA-DQB1 126Q(-)	total
CIAG	1,235	2,195	3,430
CIAG (-)	10,623	85,947	96,570
Total	11,858	88,142	100,000



	HLA-B 158T/HLA-DQB1 126Q(+)	HLA-B 158T/HLA-DQB1 126Q(-)	Sub total
CIA	287 (~23%)	413	700
CIG	948 (~77%)	1,782	2,730
Sub total	1,235 (100%)	2,195	3,430

set "CIAG prevention rate" = 0.3

$$1,235 \times 0.3 = 371$$

if we prevent CIG in subjects with HLA-B 158T/HLA-DQB1 126Q(-), a maximum ~77% CIAG prevention rate can be obtained.

Expected proportion by "HLA-guided treatment schedule"

	HLA-B 158T/HLA-DQB1 126Q(+)	HLA-B 158T/HLA-DQB1 126Q(-)	Sub total'
CIA	287	413	700
CIG	577	1,782	2,359
Sub total	658	2,195	3,059

(~11% reduction)

Supplementary Fig. 1 CIAG prevention rate

(A) for Japanese population and (B) for the UK population.

CIAG: clozapine-induced agranulocytosis/granulocytopenia, CIA: clozapine-induced agranulocytosis, CIG: clozapine-induced granulocytopenia.

a maximum ~70% CIAG prevention rate can be obtained using Bayes' theorem:

e.g. Japanese population

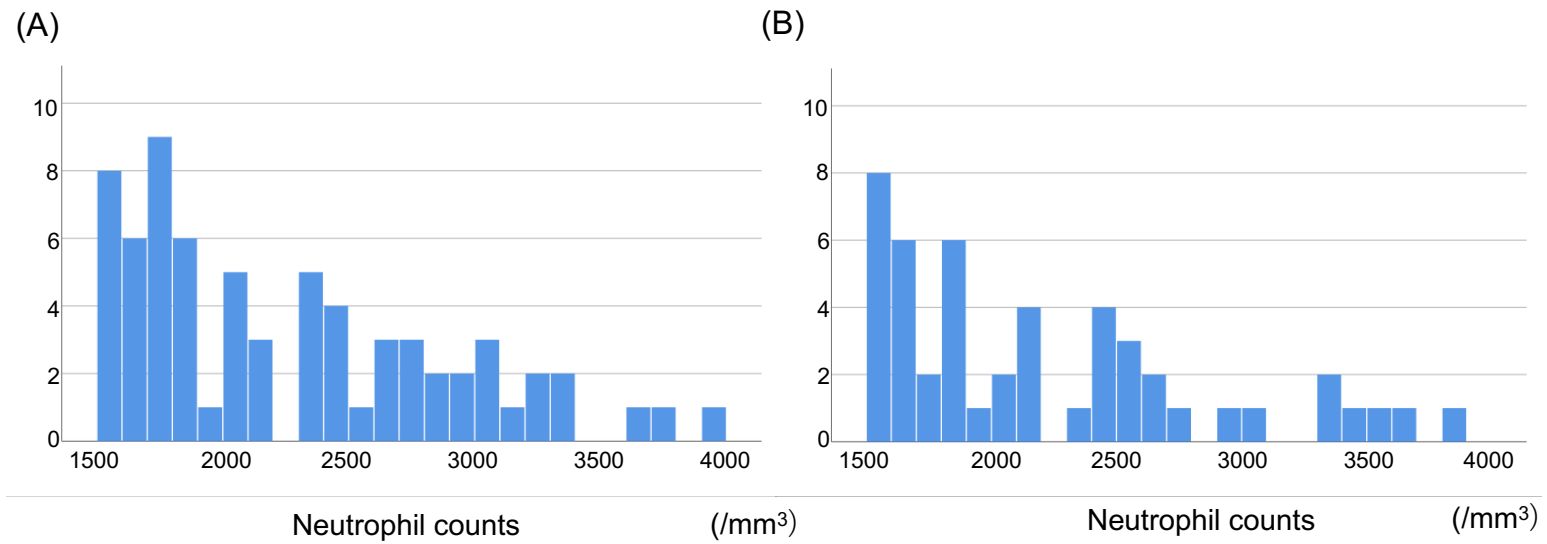
$$\begin{aligned} \text{Probability(CIA|HLA - B * 59: 01)} &= \frac{\text{Probability(CIA)} \times \text{Probability(HLA - B * 59: 01|CIA)}}{\text{Probability(HLA - B * 59: 01)}} \\ &= \frac{\text{Prevalence(CIA)} \times \text{"sensitivity for CIA"}}{\text{phenotype frequency of HLA-B*59:01(discussed below)}} = \frac{0.01088 \times 0.364}{0.0396} = 0.10 \end{aligned}$$

$$\begin{aligned} \text{Probability(CIG|HLA - B * 59: 01)} &= \frac{\text{Probability(CIG)} \times \text{Probability(HLA - B * 59: 01|CIA)}}{\text{Probability(HLA - B * 59: 01)}} \\ &= \frac{\text{Prevalence(CIG)} \times \text{"sensitivity for CIG"}}{\text{phenotype frequency of HLA-B*59:01(discussed below)}} = \frac{0.04352 \times 0.293}{0.0396} = 0.223 \end{aligned}$$

thus,

*Estimated proportion of CIG in CIAG for subjects with HLA - B * 59: 01*

$$= \frac{0.223}{0.10 + 0.223} = 0.69$$

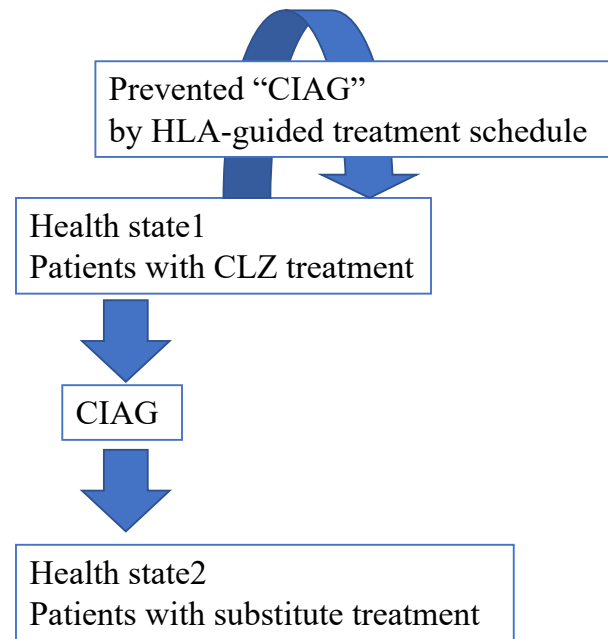


Supplementary Fig. 2 Absolute neutrophil counts (ANC) of CIAG subjects in Japan

(A) CIA, (B) CIG. X axis indicates bin for minimum neutrophil counts before onset of CIA or CIG (within six months after clozapine initiation) and Y axis indicates number of subjects.

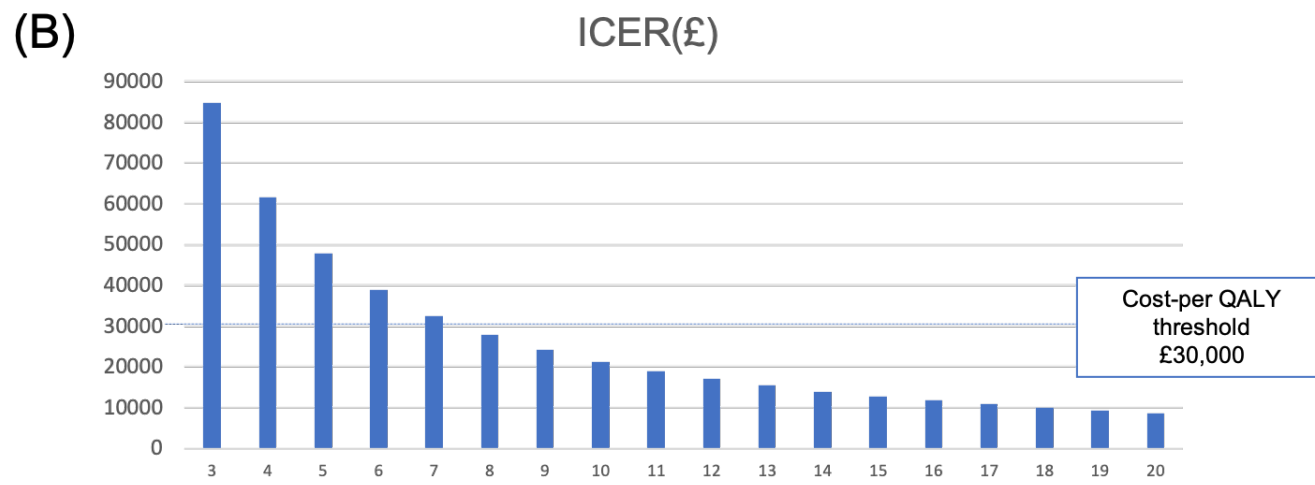
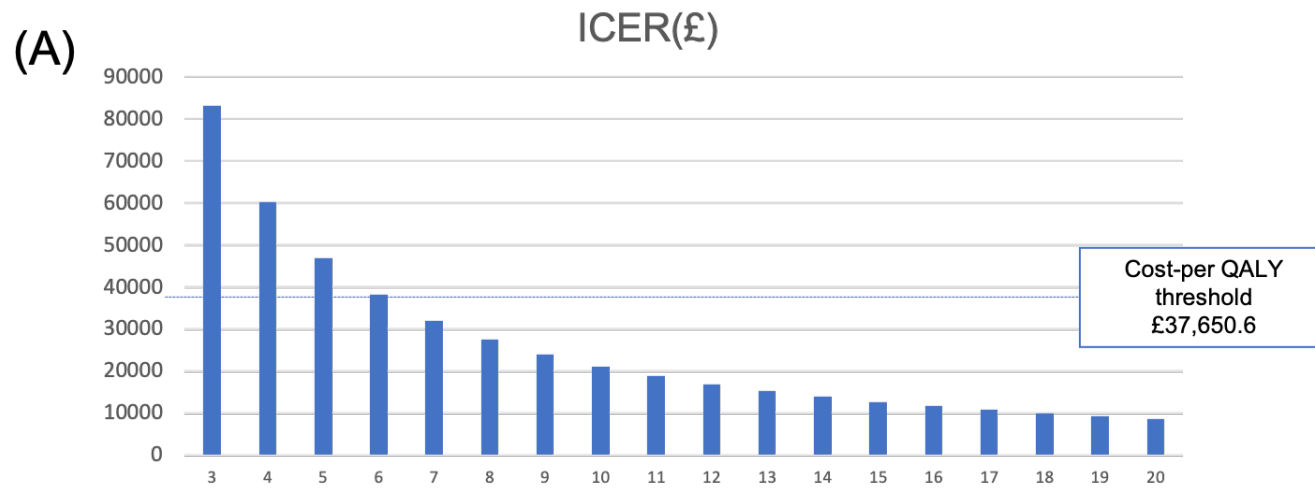
CIAG: clozapine-induced agranulocytosis/granulocytopenia, CLZ: clozapine

HLA-guided treatment schedule



Supplementary Fig. 3 Markov model schematic

CIAG: clozapine-induced agranulocytosis/granulocytopenia, CLZ: clozapine



Supplementary Fig. 4 Relationship between the incremental cost-effectiveness ratios (ICERs) and time-horizons