Supplementary appendix to: Non-identifiability in model calibration and implications for medical decision making

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To illustrate the potential issue of non-identifiability and the application of collinearity analysis to a more realistic modeling set-up, we developed a state-transition model (STM) of the natural history of colorectal cancer (CRC) implemented in discrete annual cycles based on a model originally proposed by Wu et al., 2006.[1]

Natural history model of colorectal cancer

The STM of the natural history of CRC has nine health states: normal (N), small adenoma (SA, adenoma smaller than or equal to 1 cm in size), large adenoma (LA, adenoma larger than 1 cm in size), early CRC (E, Stages I and II), preclinical early CRC (PreE) , late CRC (L, Stages III and IV), preclinical late CRC (PreL), death of CRC (DCRC) and death of other causes (DOC). The progression between states follow a continuous-time age-dependent Markov process. Figure 1 shows the state-transition diagram of the NHM of CRC.

The model has two age-dependent transition intensities (i.e., transition rates), $\lambda_1(a)$ and $\mu(a)$, that govern the age of onset of adenomas and all-cause mortality, respectively. Following Wu et al., 2006.[1], we specify $\lambda_1(a)$ as a Weibull hazard with the following specification

$$\lambda_1(a) = lga^{g-1},$$

where l and g are the scale and shape parameters, respectively. The model has seven time-homogeneous annual transition rates that describe the dynamics of adenoma growth, λ_2, transition to preclinical early CRC, λ_3, and preclinical late CRC, λ_4, to clinical early and late CRC, λ_5 and λ_6, respectively, and death from early and late CRC, λ_7 and λ_8, respectively. The whole continuous-time age-dependent STM of the natural history of CRC can be represented by the following age-dependent 9×9 transition intensity matrix, $Q(a)$

$$\mathrm{Q(a)} = \begin{array}{c} \\ N \\ SA \\ LA \\ PreE \\ PreL \\ E \\ L \\ DCRC \\ DOC \end{array} \begin{array}{c} \begin{array}{ccccccccc} N & SA & LA & PreE & PreL & E & L & DCRC & DOC \end{array} \\ \begin{pmatrix} -(\lambda_1(a)+\mu(a)) & \lambda_1(a) & 0 & 0 & 0 & 0 & 0 & 0 & \mu(a) \\ 0 & -(\lambda_2+\mu(a)) & \lambda_2 & 0 & 0 & 0 & 0 & 0 & \mu(a) \\ 0 & 0 & -(\lambda_3+\mu(a)) & \lambda_3 & 0 & 0 & 0 & 0 & \mu(a) \\ 0 & 0 & 0 & -(\lambda_4+\lambda_5+\mu(a)) & \lambda_4 & \lambda_5 & 0 & 0 & \mu(a) \\ 0 & 0 & 0 & 0 & -(\lambda_6+\mu(a)) & 0 & \lambda_6 & 0 & \mu(a) \\ 0 & 0 & 0 & 0 & 0 & -(\lambda_7+\mu(a)) & 0 & \lambda_7 & \mu(a) \\ 0 & 0 & 0 & 0 & 0 & 0 & -(\lambda_8+\mu(a)) & \lambda_8 & \mu(a) \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \end{array}$$

To translate $Q(a)$ to discrete time, we compute the annual-cycle age-dependent transition probability matrix, $P(a,t)$, using the Kolmogorov differential equations[2]

$$P(a,t) = \mathrm{Exp}(tG(a)),$$

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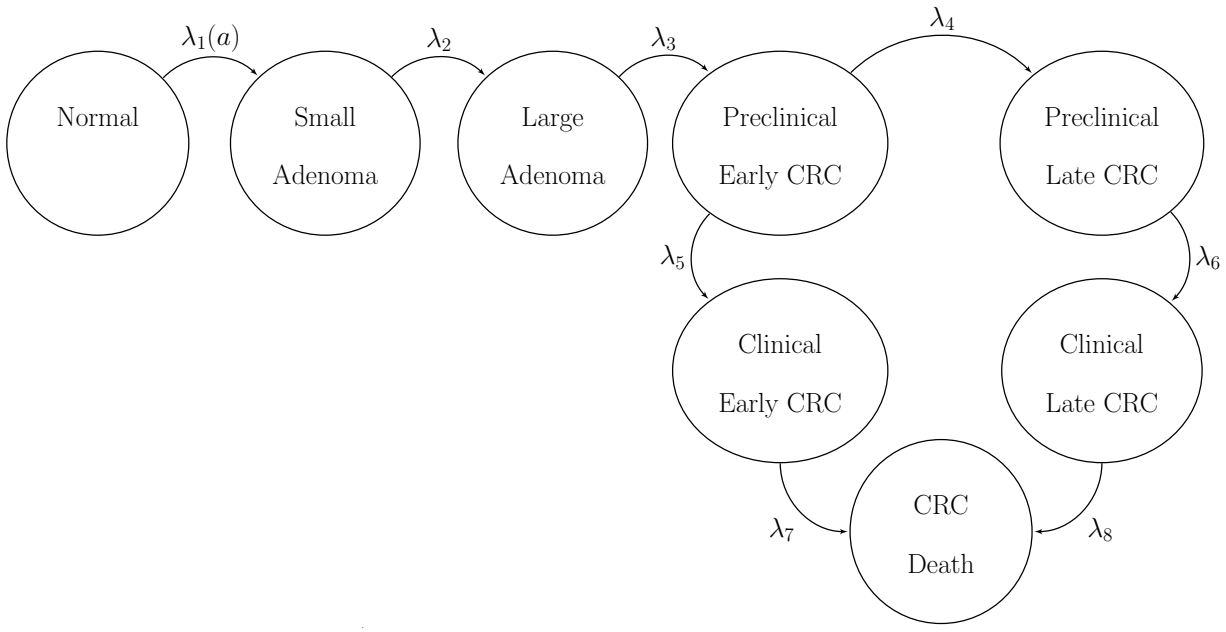

Figure 1: State-transition diagram of the natural history model of colorectal cancer

where $t = 1$ and Exp() is the matrix exponential. In practice, Exp() is difficult to calculate analytically on models with similar complexity to the one described in this section. To compute Exp() on the NHM of CRC, we used the function `MatrixExp` of the R package `msm`[5], which uses eigensystem decomposition, or, if there are repeated eigenvalues, the method of Padé approximants[6].

The model simulates the natural history of CRC of a hypothetical cohort of 50-year-old women in the US over a lifetime. The simulated cohort is at risk of all-cause mortality from all health states. We obtained all-cause mortality, $\mu(a)$, from 2014 US life tables[7].

Calibration of natural history model of colorectal cancer

In total, the natural history model (NHM) of CRC has 11 parameters. For the purposes of illustrating non-identifiability in the calibration of this model, we assume that all but two of these parameters are uncertain and need to be calibrated. We assume that CRC mortality in early and late stages, λ_7 and λ_8, respectively, could be obtained from cancer population registries (e.g., SEER in the US.), so there is no need to calibrate these. The description of the parameters of the NHM of CRC are shown in Table 1.

Table 1: Table of parameters of the natural history model of CRC.

Symbol	**Description**	**Value**	**Calibrated**	**Source**
l	Scale parameter of Weibull hazard	2.86e-06	Yes	[1]
g	Shape parameter of Weibull hazard	2.78	Yes	[1]
λ_2	Small adenoma to large adenoma	0.0346	Yes	[1]
λ_3	Large adenoma to preclinical early CRC	0.0215	Yes	[1]
λ_4	Preclinical early to preclinical late CRC	0.3697	Yes	[1]
λ_5	Preclinical early to clinical early CRC	0.2382	Yes	[1]
λ_6	Preclinical late to clinical late CRC	0.4852	Yes	[1]
λ_7	CRC mortality in early stage	0.0302	No	[1]

Symbol	Description	Value	Calibrated	Source
λ_8	CRC mortality in late stage	0.2099	No	[1]
$p_{adenoma}$	Prevalence of adenoma at age 50	0.27	Yes	[8]
p_{small}	Proportion of small adenomas at age 50	0.71	Yes	[1]

Calibration targets

To calibrate the parameters of the NHM of CRC, we conducted a confirmatory simulation where we chose a set of parameters based on plausible estimates from the literature and generated the targets that are commonly used for these models. The values used to generate the targets are shown in Table 1. We generated four different age-specific targets, including adenoma prevalence, proportion of small adenomas and CRC incidence for early and late stages, which resemble commonly used calibration targets for this type of models[9].

To generate the targets, we stochastically simulated different 50-year-old women by running the NHM of CRC as a microsimulation[11] over a lifetime. Similar to the cancer relation survival model in the main text, we used the information of the simulated individuals to estimate the targets y_t with their corresponding standard error σ_t. To account for different variations in the amount of data on different calibration targets, we simulated different numbers of individuals, N, for adenoma-related ($N = 500$) and cancer incidence ($N = 100,000$) targets. The generated age-specific targets for adenoma prevalence and proportion of small adenomas are shown in Figure 2 and the CRC incidence for early and late stages in Figure 3.

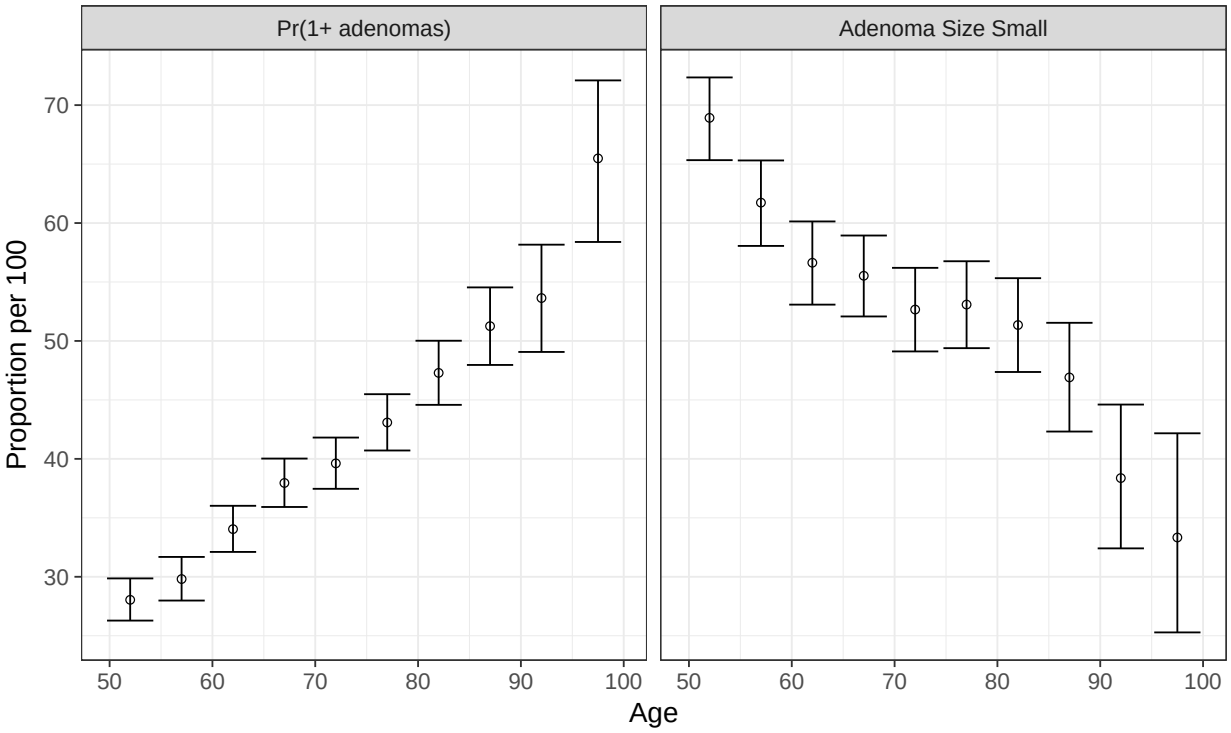

Figure 2: Calibration targets of prevalence of adenoma ("Pr(1+ adenomas)") and proportion of adenomas that are small ("Adenoma size small")

As a summary measure of the discrepancy between the corresponding model outputs, ϕ_t, and the targets, y_t, we use a likelihood function assuming the targets were normal deviations from the model outputs.

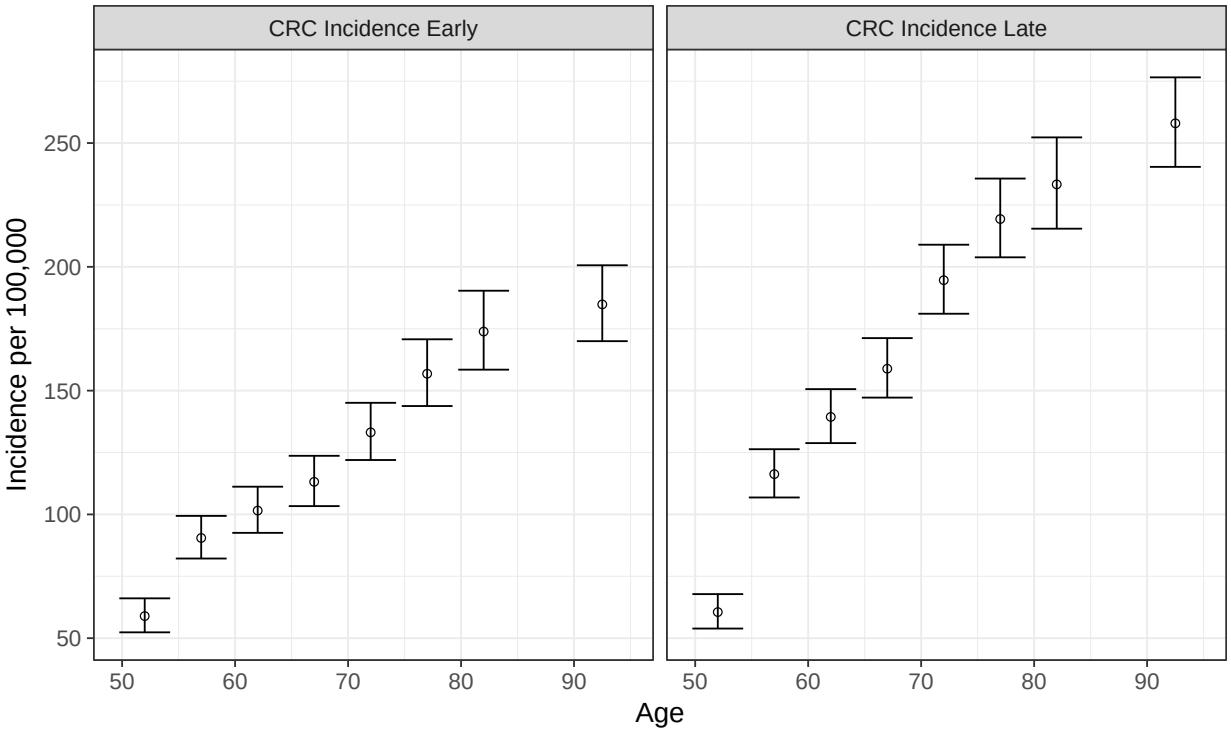

Figure 3: Calibration targets of CRC incidence for early and late stages

Identifiability analysis

We performed an identifiability analysis of the NHM of CRC by computing a collinearity index, γ, on all possible combinations of the 9 calibrated parameters for different combinations of targets using the R package `FME`[12]. It took less than one second to compute γ on all possible combinations of parameters.

Figures 4, 5 and 6 show the collineariy index for all possible combinations of parameters for multiple combinations of types of targets. Using different types and number of targets alter the number of parameters that could potentially be identifiable assuming that a parameter set is identifiable if $\gamma \leq 15$.[13,14] For example, when we only consider adenoma-related targets, such as adenoma prevalence and proportion of small adenomas, we can only estimate 12 different parameter sets of up to five different parameters while making the model calibration identifiable (Figure 4).

When only CRC incidence-related targets are used, there are 34 different parameter sets of up to five different parameters that could be identifiable (Figure 5).

Using all targets, it is possible to uniquely estimate only two different parameter sets of up to 8 parameters. Even with all the targets, it is not possible to define an identifiable calibration problem for all the model parameters, which have a combined collinearity index of 110 (Figure 6).

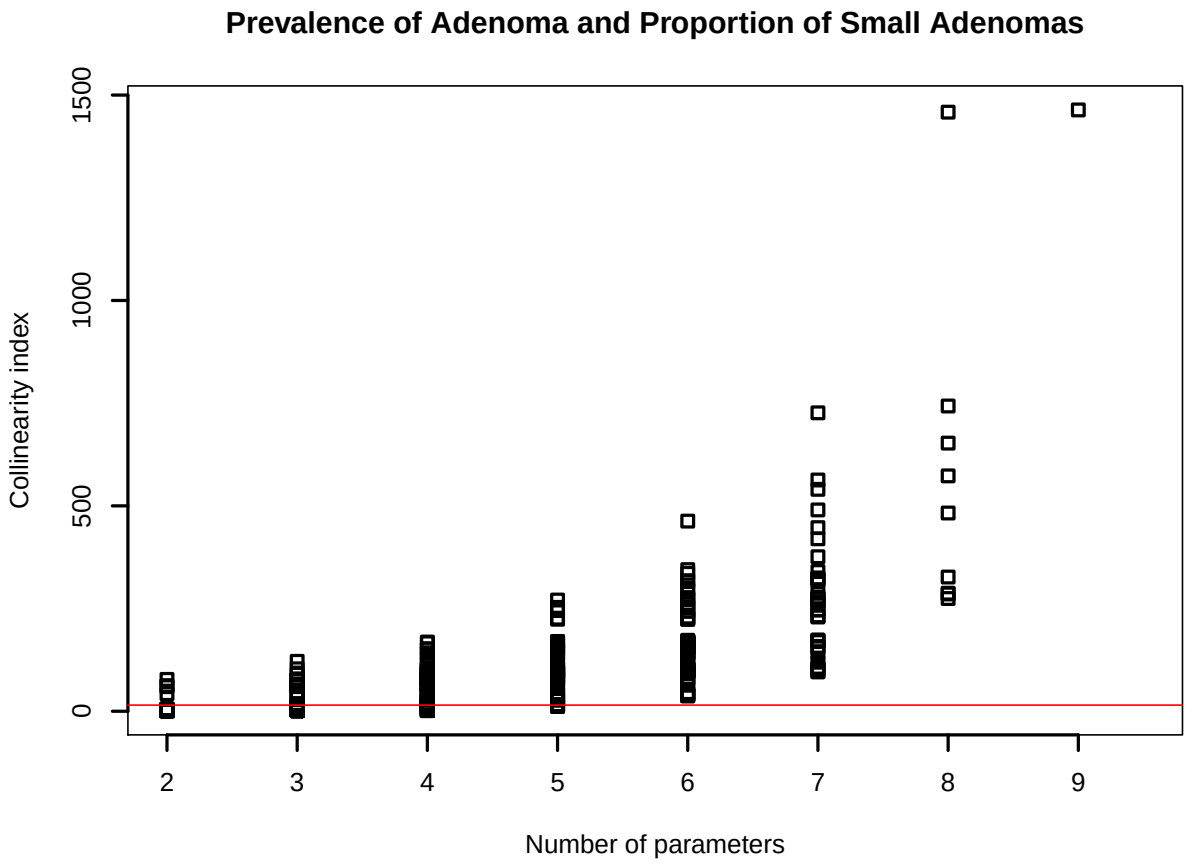

Figure 4: Collinearity index for all possible combinations of parameters using only adenoma prevalence and proportion of small adenomas (red solid vertical line indicates a collinearity index of 15)

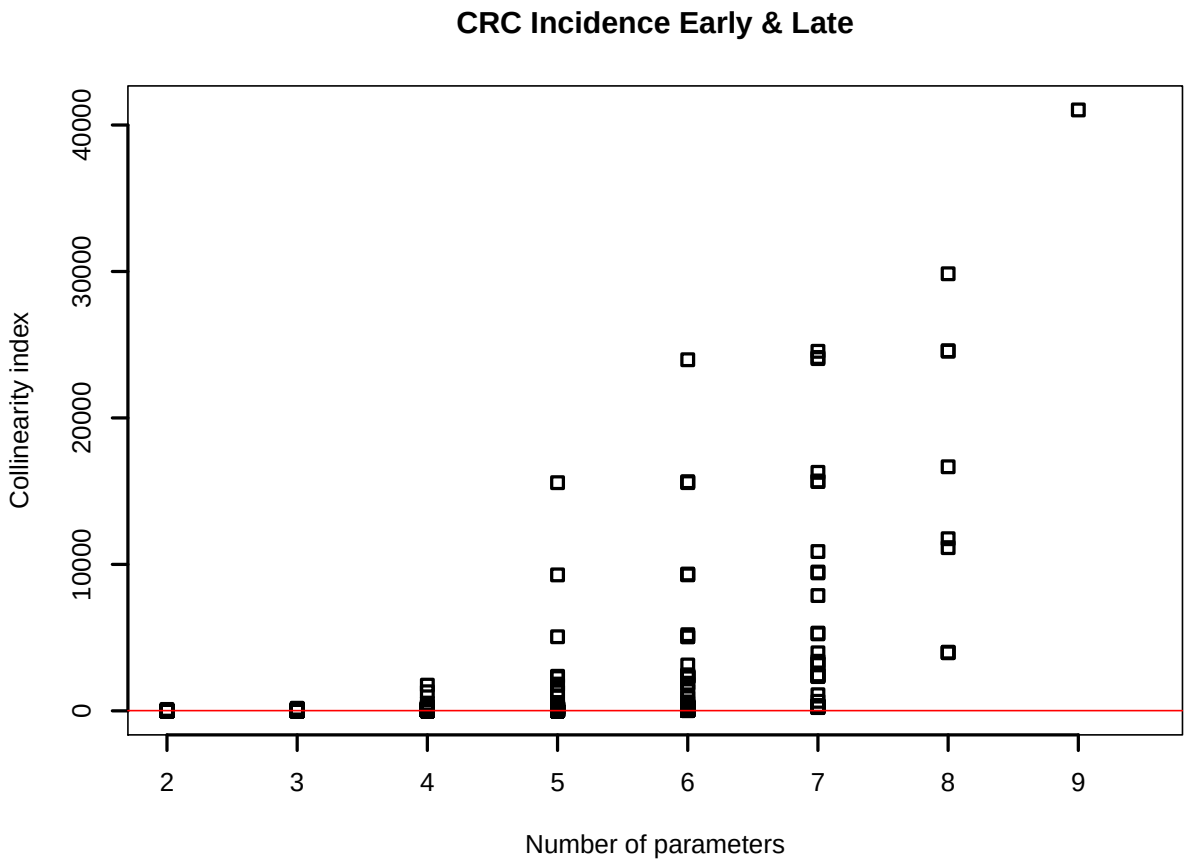

Figure 5: Collinearity index for all possible combinations of parameters using only CRC incidence of late and early stages (red solid vertical line indicates a collinearity index of 15)

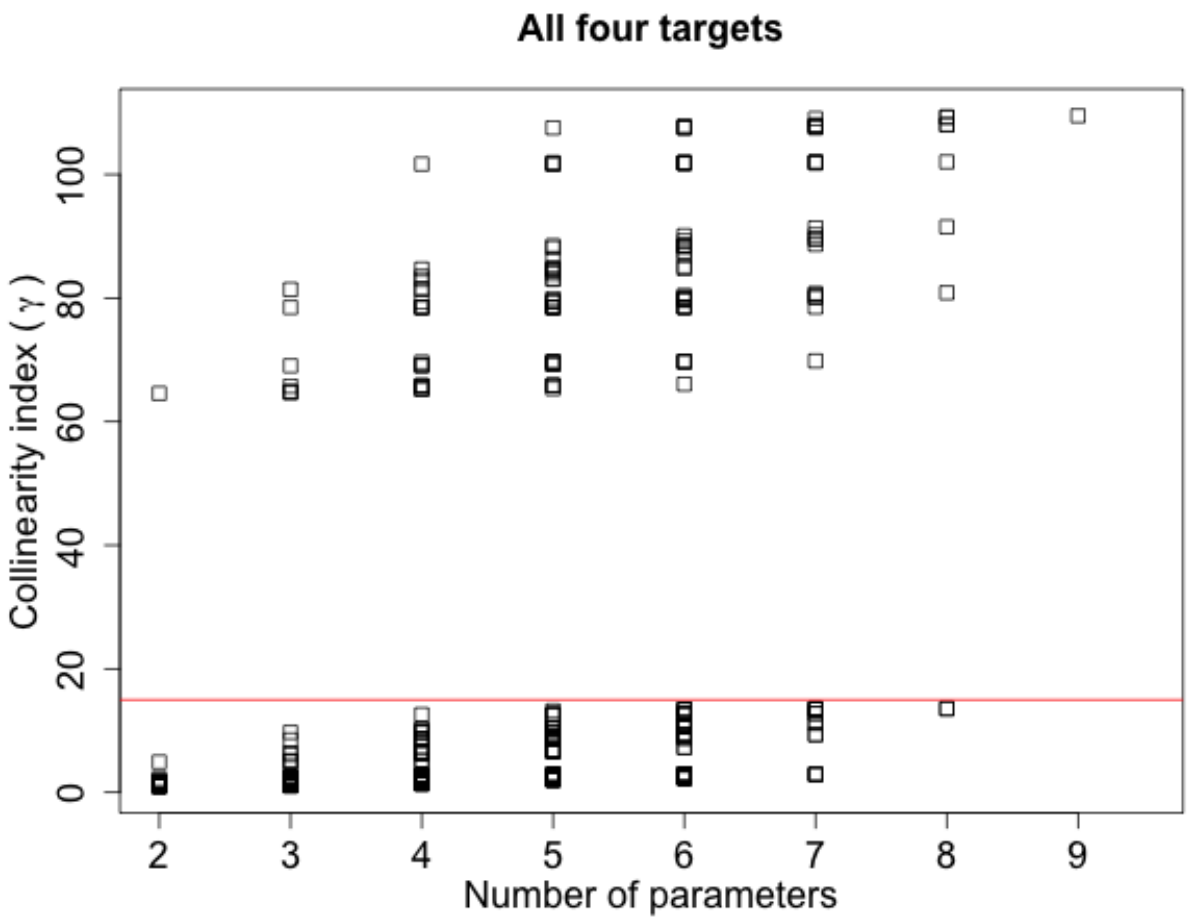

Figure 6: Collinearity index for all possible combinations of parameters using all four targets (red solid vertical line indicates a collinearity index of 15)

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