Growth prediction model for abdominal aortic aneurysms

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Abstract

Background: The most relevant determinant in scheduling monitoring intervals for abdominal aortic aneurysms (AAAs) is maximum diameter. The aim of the study was to develop a statistical model that takes into account specific characteristics of AAA growth distributions such as between-patient variability as well as within-patient variability across time, and allows probabilistic statements to be made regarding expected AAA growth.

Methods: CT angiography (CTA) data from patients monitored at 6-month intervals with maximum AAA diameters at baseline between 30 and 66 mm were used to develop the model. By extending the model of geometric Brownian motion with a log-normal random effect, a stochastic growth model was developed. An additional set of ultrasound-based growth data was used for external validation.

Results: The study data included 363 CTAs from 87 patients, and the external validation set comprised 390 patients. Internal and external cross-validation showed that the stochastic growth model allowed accurate description of the distribution of aneurysm growth. Median relative growth within 1 year was 4.1 (5–95 per cent quantile 0.5–13.3) per cent. Model calculations further resulted in relative 1-year growth of 7.0 (1.0–16.4) per cent for patients with previously observed rapid 1-year growth of 10 per cent, and 2.6 (0.3–8.3) per cent for those with previously observed slow growth of 1 per cent. The probability of exceeding a threshold of 55 mm was calculated to be 1.78 per cent at most when adhering to the current RESCAN guidelines for rescreening intervals. An online calculator based on the fitted model was made available.

Conclusion: The stochastic growth model was found to provide a reliable tool for predicting AAA growth.

Introduction

Abdominal aortic aneurysm (AAA) is an important cause of death among people over 55 years of age and is responsible for more than 1.7 million deaths per year worldwide (CDC WISQARS https://www.cdc.gov/injury/wisqars/index.html, UK Office for National Statistics, Swedish National Board of Health and Welfare). This is a reason why AAA screening has been adopted in many healthcare systems for men, but not women1. Owing to its chronic inflammatory nature, it may well take 7–14 years for a small AAA of 3 cm maximum diameter to grow to 5–5.5 cm, which is the indication for surgery2. The appropriate timing of follow-up visits depends on the current AAA size and the expected growth rate because other methods of predicting growth and AAA rupture have proven unreliable3. Accurate statistical models for AAA growth in a defined patient population, and ultimately for individual patients, are required to plan appropriate follow-up visits. The established measure of AAA size and growth is the maximum diameter, which can be determined using ultrasound imaging or CT angiography (CTA).

The established RESCAN study2 quantified the average AAA growth across a patient population and its results have been adopted in some clinical guidelines4. However, to describe the heterogeneity in growth between patients and to calculate the risk for an individual patient experiencing critically fast AAA growth, tail quantiles of the growth rate distribution, such as the 95 per cent quantile, are of main interest. In contrast to estimators of average growth rates, estimators of tail quantiles are typically less robust with respect to model misspecifications.

The objective of this study was to develop a stochastic growth model that adequately considers known properties of the natural growth of AAAs. In particular, the aim was for the model to satisfy the following criteria: absolute growth depends on AAA size5 (criterion 1), growth rates may vary in individual patients across time (within-patient heterogeneity)6,7 (criterion 2), and growth...
rates may vary between patients (between-patient heterogeneity) (criterion 3). Furthermore, the model should be applicable independently of different timings of first AAA measurements in different patients (criterion 4), and self-consistent when applied to time series of AAA measurements (criterion 5). The model was established and validated using a set of longitudinal CTA measurements of maximum AAA diameter obtained from a contemporary sample of patients who underwent regular CTA at 6-month intervals. For further validation, an external set of ultrasound-based growth data was used. As a second outcome, the growth distribution of maximum AAA diameter based on the sample data was quantified. Furthermore, the estimated risks of exceeding critical AAA sizes within different time spans for different initial maximum diameters were calculated, and the current recommendations for screening intervals were evaluated in the model.

Methods

Study population

Patients with known or newly diagnosed AAA visiting the outpatient clinic at a tertiary university hospital (Division of Vascular Surgery, Department of General Surgery, General Hospital of Vienna, Medical University of Vienna, Vienna, Austria) between 2014 and 2019 were included prospectively. Patients with a recent malignancy or chemotherapy (within 1 year), autoimmune disease, and organ transplantation were excluded from the analysis. This study was defined as an observational study, approved by the Vienna General Hospital Local Ethics Committee with licence number 1729/2014. It adhered to the principles of the Declaration of Helsinki and STROBE guidelines, and was registered at ClinicalTrials.gov (NCT03507413). The study is reported in line with the TRIPOD statement. All patients gave informed consent before participation in the study. The morphometric growth analysis was performed at 6-month intervals for up to 5 years. For CTA, a Somatom Flash® or Somatom Force instrument (Siemens, Erlangen, Germany) was used with tube voltage settings of 120 or 100 kV, and a tube current of 120 ref mA (collimation 2 x 64 x 0.6 mm). Images reconstructed in 1-mm slices were used for multiplanar reconstructions. Leading-edge-to-leading-edge diameter in axial corrected matter was defined as maximum diameter. Morphometric AAA analysis (maximum aortic diameter) was performed by two independent experts blinded to the previous CT measurement data, with a mean interobserver variability of 0.2 mm or 0.4 per cent (Table S1).

Statistical analysis

To describe patient characteristics, mean(s.d.) values were calculated for continuous variables, and absolute and relative frequencies for categorical variables.

Stochastic growth model

A stochastic growth model was developed based on the predefined criteria. To satisfy criterion 1, exponential growth was defined as core of the model. To address within-patient heterogeneity of growth rates (criterion 2), it was assumed that in each small time step a normally distributed random value with mean zero is added to the previous growth rate. This results in a geometric Brownian motion model, a well studied approach to modelling general growth processes. The model equation for a single patient is \( Y_t = \exp \left( \lambda t - \frac{1}{2} \sigma^2 t + \sigma W_t \right) \), where \( Y_t \) is the AAA size at time \( t \), \( \lambda \) is the patient-specific growth rate, \( W_t \) denotes a Brownian motion process at time \( t \), and \( \sigma \) determines the within-patient variability of the growth rate. It was further assumed that the within-patient variability is proportional to the growth rate \( \lambda \) by a scale factor \( k (\sigma = k \times \lambda) \), which is supported by Fig. S1.

To address between-patient heterogeneity in growth rates (criterion 3), the geometric Brownian motion model was extended by a log-normally distributed random effect for \( \lambda \). This assumption was supported by the empirical distribution of patient-specific growth rates (Fig. S1).

An optimization routine to estimate the model parameters via maximum likelihood was implemented in R 4.0 (R Foundation for Statistical Computing, Vienna, Austria).

Linear mixed model

For comparison, the growth of AAAs was also modelled using a linear mixed model similar to the methods used in previous studies. For a single patient, the respective model equation is \( Y_t = b_0 + b_1 \times t + \epsilon \). The regression coefficients \( b_0 \) and \( b_1 \) are assumed to be bivariate normally distributed between patients. Here, the variability of the intercept \( b_0 \) reflects the differences of initially observed AAA size between patients. The variability of the slope \( b_1 \) reflects the heterogeneity in growth rates between patients, and the correlation between the two parameters accounts for the fact that AAA growth is on average faster in patients with a larger initial AAA size. However, the model does not capture the possibility that growth may increase with time in a patient. The error term \( \epsilon \) is assumed to be normally distributed and independent for all measurements. It reflects within-patient variability to some extent. Linear mixed models were fitted using restricted maximum likelihood with the library lme4 in R 4.0.

Probabilities and quantiles

Probabilities of exceeding a certain maximum diameter and, conversely, quantiles of predicted maximum diameter distributions were calculated from the stochastic growth and linear mixed models. Computational details are available in the Supplementary material. In brief, in the stochastic growth model, given an initial maximum AAA diameter, the distribution of maximum AAA diameters at a specified later time point is an integral of log-normal distributions over the random-effect distribution for the individual growth rate. In the linear mixed model, the corresponding maximum AAA diameters have a normal distribution. Probabilities and quantiles were calculated from these distributions after plugging in maximum likelihood estimates for the required model parameters and, for the stochastic growth model, by performing numerical integration. Further details can be found in the Supplementary material. Standard errors for probabilities and quantiles were calculated using the leave-one-out jackknife method.

Model validation

Leave-one-out cross-validation was applied to assess the validity of the stochastic growth and linear mixed models. In each cross-validation round, the data set was split into a training sample, including all but one patient, and a test sample comprising data from the patient who was left out of the training sample. Each patient was left out once. In each round, the stochastic growth model and the mixed model were fitted with the training sample. The models were then used to predict the 5, 10, 25, 50, 75, 90, and 95 per cent quantiles of the distribution of the last observation of the test sample, using the first observation of the test sample as input. For each quantile, the percentage of patients for whom the observed final value was below the predicted quantile was...
determined and compared with the nominal quantile levels. For a model that perfectly predicts growth distribution, these two quantities should be identical up to sampling variation. The expected sampling variation was assessed in terms of the standard error for proportions as derived from the normal approximation of the binomial distribution. In a supplementary analysis, the same assessment was made including all observations after each patient’s initial measurement.

**External validation**

External validation was undertaken using a data set from Uppsala, Sweden, of longitudinal ultrasound-based measurements of maximal AAA leading-edge-to-leading-edge diameter in patients with a screening-detected AAA. The reported measurement variability was 2.0 (± 4.0) mm with a coefficient of variability of 5.0 per cent. The patients originated from two population-based screening cohorts; all 65-year-old men and all 70-year-old women in the county of Uppsala were invited for an ultrasound examination of the aorta. Some 83.7 per cent of all men accepted the invitation, and 74.2 per cent of all women attended. For each patient, the measurement time point closest to 1 year within 0.5–1.5 years after the initial observation was identified. Similarly, the measurement time point closest to 2 years within 1.5–2.5 years after the initial observation was identified. The stochastic growth model and the linear mixed model, which were fit with the Viennese data set, were used to predict the 5, 10, 25, 50, 75, 90, and 95 per cent quantiles of the growth distribution for each patient at these two measurement points, based on the maximum diameter at the initial time point and the individual time intervals. Similar to the internal cross-validation, for each quantile, the percentage of patients for whom the observed value was below the predicted quantile was determined, and compared with the respective nominal quantile levels. For further comparison of model parameters, the stochastic growth model was also fit using the validation data.

**Evaluation of prognostic properties for threshold crossing**

Use of the stochastic growth and linear mixed models as prognostic tools for the crossing of a specific threshold diameter was further assessed in a receiver operating characteristic (ROC) analysis using leave-one-out sample splitting with the study data set. For each patient with an initial maximum diameter below 55 mm, the probability of having crossed that threshold at the observed measurement time point closest to the recommended surveillance interval (3, 1 or 0.5 years respectively for initial diameters below 40 mm, or 40 mm or more, and less than 50 mm, or 50 mm or more) was calculated using models that were fitted with data from all other patients. In a ROC analysis, the calculated probabilities, based on the initial value, were used as predictor and the observed status of crossing as the outcome. The best cut-off for the predictor was determined as the value providing the largest sum of sensitivity and specificity. The same analyses were performed for all patients in whom the second measurement was below 55 mm, with surveillance intervals starting at the second time point and with probabilities calculated from refined individual growth distributions based on the first two measurements. Owing to the small number of patients whose aneurysm crossed the threshold, these analyses are considered exploratory.

**Results**

**Characteristics of patient sample**

A total of 363 CTA measurements, in 87 patients (11 women and 76 men), in whom AAA growth was monitored by CTA at regular intervals of approximately 6 months, were included in the study. The maximum AAA diameter at baseline was between 30 and 66 mm, with a median of 46 mm. The minimum, median, and maximum number of visits with CTA was two, four, and nine respectively.

**Visualization of observed and modelled AAA growth**

Time trajectories for the median absolute growth and different quantiles of the relative growth distribution in the studied patient population were estimated from the model and plotted together with the observed data (Fig. 1). The observed growth of maximum diameter was larger in patients with a larger aneurysm at the initial visit. Accordingly, median growth curves as predicted by the stochastic growth model were steeper and showed stronger curvature for larger initial maximum diameters (Fig. 1a). Individual curves of relative growth showed a right skewed distribution, with some patients exhibiting much faster growth than the vast majority. On visual inspection, the estimated quantiles of the stochastic growth model matched well with the observed distribution of individual growth curves (Fig. 1b). In contrast, the linear mixed model assumes a more symmetric distribution

| Table 1 Patient characteristics | No. of missing observations | No. of patients* |
|--------------------------------|-----------------------------|------------------|
| **Demographics**               |                             |                  |
| Age at first visit (years)†    | 0                           | 71.6(7.7)        |
| Men                            | 0                           | 76 (87)          |
| BMI (kg/m²)†                   | 1                           | 28.2(4.5)        |
| Duration of follow-up (years)† | 0                           | 1.9(1.2)         |
| **Vascular characteristics†**  |                             |                  |
| Maximum AAA diameter at first visit (mm) | 0 | 45.8(7.9) |
| Maximum thrombus at first visit (mm) | 8 | 12.2(7.9) |
| Thrombus volume at first visit (ml) | 12 | 33.2(30.4) |
| **Smoking habits**             |                             |                  |
| Never smoked                   | 0                           | 5 (6)            |
| Past smoker                    | 0                           | 52 (60)          |
| Current smoker                 | 0                           | 30 (34)          |
| Pack-years (of past and current smokers)† | 5 | 46.4(29.8) |
| **Co-morbidities**             |                             |                  |
| Hypertension                   | 0                           | 74 (85)          |
| Hyperlipidaemia                | 0                           | 72 (83)          |
| Peripheral artery disease      | 0                           | 15 (17)          |
| Coronary heart disease         | 0                           | 30 (34)          |
| Myocardial infarction          | 0                           | 20 (23)          |
| Stroke                         | 0                           | 5 (6)            |
| Diabetes mellitus              | 0                           | 20 (23)          |
| COPD                           | 0                           | 30 (34)          |
| **Medication**                 |                             |                  |
| Antiplatelet therapy           | 0                           | 78 (90)          |
| Anticoagulation therapy        | 0                           | 17 (20)          |
| Antihypertensive therapy       | 0                           | 74 (85)          |
| Lipid-lowering agents          | 0                           | 82 (94)          |
| Diabetic medication            | 0                           | 20 (23)          |

*With percentages in parentheses unless indicated otherwise; †values are mean(s.d.) Hypertension, hyperlipidaemia, peripheral artery disease, myocardial infarction, stroke, coronary heart disease, diabetes mellitus, and chronic obstructive pulmonary disease (COPD) were defined according to the American Heart Disease classification. AAA, abdominal aortic aneurysm.
191 patients (85.9 per cent men, 14.1 per cent women) an ultrasound-based measurement of maximum diameter was available between 0.5 and 1.5 years after the initial measurement. The initially measured maximum diameters were between 30 and 58 mm, with mean of 39.7 mm. For 283 patients (90.1 per cent men, 9.9 per cent women), a measurement was available between 1.5 and 2.5 years, and the initially measured maximum diameters were between 28 and 58 mm, with a mean of 36.3 mm. Hence, the external validation data set was comparable to the study data set in terms of sex distribution and initial maximum diameters. Nonetheless, the overall pattern of growth curves showed relevant differences.

In the CT-based study data set, all patients showed some increase in maximum diameter with time. In particular, the maximum diameter was larger than the initial maximum diameter at all follow-up visits for all patients. In contrast, in the ultrasound-based validation data set, a considerable number of patients showed temporary decreasing maximum diameter measurements and values below the initially observed maximum diameter (Fig. 1a). Accordingly, both the stochastic growth model and the linear mixed model that were fit with the study data set considerably overestimated the 5, 10, and 25 per cent quantiles in the validation data set at both time points considered (Table 3). The linear mixed model underestimated the 75 per cent and, to a greater extent, the 90 and 95 per cent quantiles, at both time points. The stochastic growth model showed some underestimation of these quantiles at the 1-year time point; however, it showed very good agreement for the 2-year time point. Both models performed reasonably well in estimating the median.

The larger variability within individual AAA growth curves in the validation data set compared with the study data set may be attributed, at least in part, to the different measurement methods, as ultrasound-based measurements are expected to be less precise than those based on CTA. This assumption was supported by the model parameters of the stochastic growth model when fitted to the validation data set. The values for mean growth rate and between-patient variability were almost identical to the corresponding estimates obtained with the study data set, but the value of the scale factor describing within-patient variability was larger (Table S3 and estimated model parameters in the Supplementary material). Finally, quantiles that were predicted from the model fit to the validation data suggested an accurate model fit (Fig. 2b). Hence, the proposed parametrization of

### Table 2 Leave-one-out cross validation

| Quantile level (%) | % below predicted quantile |
|--------------------|----------------------------|
|                    | SGM | LMM | Standard error |
| 5                  | 1.1 | 1.1 | 2.3 |
| 10                 | 6.9 | 8.0 | 3.2 |
| 25                 | 18.4| 20.7| 4.6 |
| 50                 | 41.4| 56.3| 5.4 |
| 75                 | 74.7| 73.6| 4.6 |
| 90                 | 92.0| 85.1| 3.2 |
| 95                 | 96.6| 89.7| 2.3 |

Values are the percentage of patients for whom the observed final abdominal aortic aneurysm (AAA) maximum diameter was below the 5, 10, 25, 50, 75, 90 or 95 per cent quantile that was predicted individually for each patient using the stochastic growth model (SGM) or the linear mixed model (LMM). Standard errors for the percentages were calculated under the assumption of a perfect prediction model and are shown to assess the expected impact of sampling variability on deviations from the nominal quantile level of individual growth curves and does not allow for the modelled within-patient variability to increase with time. Consequently, the linear mixed model overestimated the median growth and underestimated quantiles at the upper end of the growth distribution, thereby underestimating the potential for individuals with rapidly growing aneurysms (Fig. 1c).

### Model validation

The leave-one-out cross validation showed good agreement of the predictions of the stochastic growth model with the observed data. For risk assessment, the upper-tail quantiles, such as the 75, 90, and 95 per cent values, are most relevant. The stochastic growth model performed particularly well for the prediction of these quantiles. In contrast, the linear mixed model performed well only up to the 75 per cent quantile of the maximum diameter, but underestimated the 90 and the 95 per cent quantiles (Table 2 and Table S2).

In the external validation data set (390 patients in total), for 191 patients (85.9 per cent men, 14.1 per cent women) an ultrasound-based measurement of maximum diameter was available between 0.5 and 1.5 years after the initial measurement. The initially measured maximum diameters were between 30 and 58 mm, with mean of 39.7 mm. For 283 patients (90.1 per cent men, 9.9 per cent women), a measurement was available between 1.5 and 2.5 years, and the initially measured maximum diameters were between 28 and 58 mm, with a mean of 36.3 mm. Hence, the external validation data set was comparable to the study data set in terms of sex distribution and initial maximum diameters. Nonetheless, the overall pattern of growth curves showed relevant differences.

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the stochastic growth model allows sufficient flexibility to also cover data with larger variability.

**Estimated growth of maximum AAA diameter in relation to monitoring recommendations**

Using the stochastic growth model, a mean growth rate of maximum AAA diameter of 5.2 per cent per year was estimated; for example, in a patient with a maximum AAA diameter of 40 mm, this translates into an expected absolute growth of 2.1 mm within the next year. The estimated median growth rate was 4.1 (i.q.r. 2.3–6.8) per cent. The estimated range between the 5 and 95 per cent quantiles was a growth of 0.5–13.3 per cent. A comprehensive description of the estimated growth distribution is given in Table 4. The estimated model parameters are shown in Table S3, together with a brief discussion of their interpretation.

**Assessment of monitoring recommendations**

European clinical guidelines for the management of AAA recommend rescreening of aneurysms with diameters up to 30, 40 or 50 mm within 3, 1 or 0.5 years respectively. The stochastic growth model was used to estimate, for aneurysms with 30, 40 or 50 mm maximum diameter, the probability of exceeding a threshold maximum diameter of 50, 55 or 60 mm within the rescreening time recommended by the guideline (Table 5). In general, when adhering to the European clinical guideline, the probabilities of exceeding the threshold were small, in the order of a few patients per 1000. The calculated probability of exceeding 55 mm within the recommended interval was largest for patients with a maximum diameter of 50 mm, with a value of 1.78 per cent. For comparison, the probabilities in this setting associated with smaller rescreening intervals of 3 or 4 months were 0.5 and 0.2 per cent respectively (Table 5). The calculated probability of exceeding 50 mm within the recommended interval was largest for patients with a maximum diameter of 30 mm, at 0.8 per cent. The calculated probability of exceeding 60 mm within the recommended interval was also largest for patients with a maximum diameter of 30 mm, at 0.16 per cent.

**Refined estimation of growth distribution depending on previous measurements**

When using a random-effects model such as the stochastic growth model to predict AAA growth in an individual patient,
Previous measurements may be included by calculating the respective conditional growth distribution. The effect of subsequently updating predictions is illustrated in Fig. 3. For these patients, the updated growth distributions resulted in considerably reduced variance and narrower prediction intervals compared with the growth distribution of the overall population. Additionally, the refined distributions were shifted towards lower or greater average growth rates, reflecting the respective information from previous growth. Some uncertainty remains, as the model still accounts for individual growth rates, which may change with time. In all three patients, the observed maximum diameter values were within the range of the updated 5 and 95 per cent quantiles. When performing analogous predictions and updating using the linear mixed model, the predicted distributions were shifted towards smaller values and included declining diameters to a greater extent (Fig. S3). However, with subsequent updating, the modelled distributions of both models tended to become more similar, as the influence of model-specific assumptions on the random-effect distribution weakened, once the individual slope could be determined by sufficient data. After updating, the linear mixed model in some instances predicted a wider distribution than the stochastic growth model, because a constant error term that is not time-dependent was always added, whereas in the stochastic growth model the modelled variability was smaller for short time intervals and increased with time.

A systematic assessment of updated growth distributions using the stochastic growth model when two previous AAA

### Table 4 Estimated distribution of 1-year growth of maximum abdominal aortic aneurysm diameter calculated from novel stochastic growth model

| Growth          | Initial value | Mean increase | Quantiles of 1-year growth distribution |
|-----------------|---------------|---------------|----------------------------------------|
|                 |               |               | 5% | 10% | 25% | Median | 75% | 90% | 95% |
| Relative (%)    | 100           | 5.2 (0.4)     | 0.5 (0.2) | 1.2 (0.2) | 2.3 (0.2) | 4.1 (0.3) | 6.8 (0.5) | 10.4 (0.9) | 13.3 (1.3) |
| Absolute (mm)   | 30            | 1.6 (0.1)     | 0.2 (0.1) | 0.3 (0.0) | 0.7 (0.1) | 1.2 (0.1) | 2 (0.1) | 3.1 (0.3) | 4.0 (0.4) |
| Absolute (mm)   | 40            | 2.1 (0.2)     | 0.2 (0.1) | 0.5 (0.1) | 0.9 (0.1) | 1.7 (0.1) | 2.7 (0.2) | 4.1 (0.4) | 5.3 (0.5) |
| Absolute (mm)   | 50            | 2.6 (0.2)     | 0.3 (0.1) | 0.6 (0.1) | 1.2 (0.1) | 2.1 (0.1) | 3.4 (0.2) | 5.2 (0.5) | 6.6 (0.7) |

Values in parentheses are standard errors. Mean and median increase, and selected quantiles of growth distribution, are shown for a starting value of 100 per cent (showing relative growth as a percentage) and for starting values of 30, 40, and 50 mm (showing absolute growth in millimetres).

### Table 5 Estimated risk of maximum abdominal aortic aneurysm diameter exceeding 50, 55 or 60 mm within selected surveillance intervals for current diameters of 30, 40, and 50 mm

| Initial maximum diameter (mm) | Time until next surveillance (years) | Estimated % of patients exceeding threshold |
|------------------------------|-------------------------------------|-------------------------------------------|
|                              |                                     | 50-mm threshold | 55-mm threshold | 60-mm threshold |
| 30                           | 3                                   | 0.80 (0.48)     | 0.34 (0.24)     | 0.16 (0.13)   |
| 40                           | 1                                   | 0.48 (0.29)     | 0.07 (0.06)     | 0.02 (0.02)  |
| 50                           | 0.5                                 | –               | 1.78 (0.71)     | 0.09 (0.07)  |
| 50                           | 0.33                                | –               | 0.50 (0.27)     | 0.02 (0.02)  |
| 50                           | 0.25                                | –               | 0.20 (0.13)     | 0 (0.01)     |

Values in parentheses are standard errors.
measurements with an interval of 1 year were available is reported in Table 6. The relative growth within 1 year was estimated, assuming that the relative growth in the previous year was between 1 and 13 per cent. For example, in subjects with a relative growth of 4 per cent in the previous year (which is close to the estimated population median, Table 4), the estimated median for the relative growth in the subsequent year remained almost unchanged at 3.8 (5–95 per cent quantile 0.6–10.0) per cent. In contrast, model calculations indicated 1-year growth of 7.0 (1.0–16.4) per cent for patients with previously observed fast 1-year growth of 10 per cent, and 2.6 (0.3–8.3) per cent for patients with previously observed slow growth of 1 per cent.

**Evaluation of prognostic properties for threshold crossing**

For patients with an initial maximum diameter below 40 mm, 40 mm or above and less than 50 mm, or 50 mm and over and less than 55 mm, the observed measurement time point closest to the recommended surveillance interval was, on average, after 2.2, 1.1, and 0.5 years. Both models showed similar performance in discriminating between patients whose aneurysms did or did not cross the 55-mm maximum diameter threshold at these time points, with high sensitivity and specificity (Table 7, ROC curves in Fig. S4). With predictions based on the initial diameter, both models correctly classified five of seven patients with crossing. In the two patients who were not classified correctly, the aneurysm grew by 7.0 per cent within 6 months, from 51.6 to 55.2 mm, and by 12.8 per cent within 4 months, from 50.1 to 56.5 mm. The stochastic growth model attributed a crossing probability of 6 and 0.5 per cent respectively to these subjects, and the linear mixed model suggested much smaller probabilities of 1.5 and 0.0004 per cent. When predictions were based on the first two measurements, both models correctly classified all remaining patients who crossed the threshold.

### Table 6 Conditional distribution of relative 1-year growth of maximum abdominal aortic aneurysm diameter, assuming that the relative growth in the previous year was between 1 and 13 per cent

| Previous 1-year growth (%) | Predicted 1-year growth (%) | 5% quantile | Median | 95% quantile |
|---------------------------|------------------------------|-------------|--------|-------------|
| 1                         |                              | 0.3 (0.1)   | 2.6 (0.3) | 8.3 (0.7)   |
| 2                         |                              | 0.4 (0.1)   | 2.8 (0.2) | 8.3 (0.6)   |
| 3                         |                              | 0.5 (0.2)   | 3.3 (0.1) | 9.0 (0.5)   |
| 4                         |                              | 0.6 (0.2)   | 3.8 (0.1) | 10.0 (0.5)  |
| 5                         |                              | 0.6 (0.2)   | 4.6 (0.1) | 11.0 (0.6)  |
| 6                         |                              | 0.7 (0.2)   | 4.9 (0.1) | 12.1 (0.7)  |
| 7                         |                              | 0.8 (0.3)   | 5.4 (0.2) | 13.2 (0.7)  |
| 8                         |                              | 0.8 (0.3)   | 5.9 (0.2) | 14.3 (0.8)  |
| 9                         |                              | 0.9 (0.3)   | 6.5 (0.2) | 15.3 (0.9)  |
| 10                        |                              | 1.0 (0.3)   | 7.0 (0.3) | 16.4 (1.0)  |
| 11                        |                              | 1.0 (0.4)   | 7.4 (0.3) | 17.5 (1.1)  |
| 12                        |                              | 1.1 (0.4)   | 7.9 (0.3) | 18.6 (1.1)  |
| 13                        |                              | 1.2 (0.4)   | 8.4 (0.4) | 19.6 (1.2)  |

Values in parentheses are standard errors. Data calculated using stochastic growth model.

### Table 7 Sensitivity and specificity of stochastic growth model and linear mixed model for crossing a 55-mm maximum diameter threshold within the recommended surveillance interval

| Crossing probability cut-off | Patients with crossing of 55-mm threshold | Patients without crossing of 55-mm threshold |
|------------------------------|------------------------------------------|---------------------------------------------|
|                             | Proportion correctly classified | Sensitivity (%) | Proportion correctly classified | Specificity (%) |
| SGM     | 0.48                          | 5 of 7            | 71 (29, 96)                  | 72 of 72       | 100 (95, 100) |
| LMM     | 0.60                          | 5 of 7            | 71 (29, 96)                  | 71 of 72       | 99 (93, 100)  |
| Updated SGM | 0.47                      | 3 of 3            | 100 (29, 100)                | 50 of 53       | 94 (84, 99)   |
| Updated LMM | 0.48                      | 3 of 3            | 100 (29, 100)                | 49 of 53       | 92 (82, 98)   |

Values in parentheses are exact 95 per cent confidence intervals. Individual probabilities of crossing are based on the initial measurement and the modelled distribution for the population (stochastic growth model, SGM, linear mixed model, LMM), or on the first two measurements and the modelled distribution conditional on the individual growth between these. Crossing is predicted when the calculated probability of crossing is equal to or larger than the respective cut-off.
The present model allows for growth rates that increase with increasing aneurysm size (criterion 1), right-skewed heterogeneity in growth rates between patients (criterion 3), and heterogeneity in growth rates in a patient across time (criterion 2). In particular, the modelled within-patient heterogeneity of growth rates allows the model to accommodate a ‘staccato’ type growth comprising alternating phases of fast and slow growth. Furthermore, the model is applicable to patients who present at different stages of disease at the initial diagnosis (criterion 4) and the proposed model is self-consistent (criterion 5). This means that, if the model is correct, it is applicable to all data points without contradictory results. Meeting these criteria is a requirement for a reliable and plausible AAA growth model. Criteria 1, 4, and 5 are natural properties of exponential growth models, which supports the use of this type of model as the basis for the present approach. Criteria 1 and 4 are also met by linear or quadratic models in which a slope term depends on the initial AAA size. However, these models fail to meet criterion 5 (Fig S2a). With the appropriate choice of a random-effect distribution, linear or quadratic models may meet criterion 3. However, previous models in the literature all used normally distributed random effects. This is not an entirely plausible assumption as this approach tends to underestimate the skewness of the distribution of growth rates across patients, and may even allow for patients with entirely negative growth21, which has not been observed in the clinical situation. Criterion 2 may in principle be captured by the residual term in common regression models. However, even given a patient-specific random effect, these residuals are neither independent nor do they have the same variance for all time points, and it is challenging to define an appropriate residual distribution for AAA growth in these models. Criterion 5 can be a particular issue when reporting mean growth rates; as the growth of AAs is not linear, these estimates depend on the observation interval and will give inherently different results when the observation interval is extended (Fig S2b). Simple mean growth rates are, however, reasonable approximations, if the observation intervals are relatively short (6–12 months), such that a linear approximation is adequate.

The observed average growth rate of 1.6 mm/year for aneurysms with a maximum diameter of 30 mm was similar to values of approximately 1–3 mm/year reported in the literature22,23. For larger aneurysms, the observed growth rates were below published values; for example, 2.6 mm/year for a maximum diameter of 50 mm compared with 3.6 mm/year in the RESCAN study4. These differences may reflect improved management of AAA growth in the more recent study cohort, in part through use of improved cardiovascular medications24. The calculated probability of exceeding 60 mm within the recommended interval was largest for patients with a maximum diameter of 30 mm, with a value of 0.16 per cent. Current European surveillance guidelines for AAA are thus supported by the prospectively collected data set and the stochastic growth model. Comparing the Austrian and Swedish data sets, the stochastic growth model estimated the relevant 75, 90, and 95 per cent quantiles within reasonable limits for the 1-year time point and with very good agreement for the 2-year time point. The linear mixed model tended to underestimate these upper-tail quantiles. However, both models performed reasonably well in estimating the median and both showed similar performance in the exploratory ROC analysis for threshold crossing.

Even though the proposed model was fitted with precise CTA data, one must take certain limitations into account. Only 87 patients (363 screening visits) were included in the study, which is a limited patient cohort. All patients were Caucasian from central Europe; larger groups with different ethnicities from all around the world would increase the value of the study. For some patients, follow-up was censored owing to surgical intervention, whereas surgery was not possible for other patients and monitoring was continued to maximum diameters above 55 mm. Although this may result in a selected patient population with larger diameters, inspection of the individual trajectories supports the assumption that the growth process behaves similarly over the full range of observed diameters. Furthermore, random-effect models, such as the stochastic growth model and the linear mixed model, are robust with respect to missing data, as long as missingness depends only on observed values (such as an observed diameter above some threshold). The risk of bias in the analyses should therefore be low. The stochastic growth model allows refined predictions for individual patients based on previous measurements of maximum AAA diameter. In addition, the effect of co-variables on AAA growth could be explored by extending the growth rate parameter of the model by an appropriate regression function. Establishing the required mathematical background and computational routines is matter of current research.

Supplementary material
Supplementary material is available at BJS online.

Funding
This work was supported by the Austrian Science Fund (SFB project F 5409-B21 assigned to C.B.).

Disclosure. The authors declare no conflict of interest.

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