# Supplementary Materials

## Table S1. Description of Costs

| Cost                                    | Description                                                                                                                                                                                                                                                                                                                                 |
|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Termination of Pregnancy**            | The unit cost of a termination of pregnancy varied based on the number of weeks of gestation (£397 for under 14 weeks, £498 for 14-20 weeks; £620 for over 20+ weeks). Feticide costs (£500.93) were applied to every TOP case that exceeded 22 weeks gestation (not inclusive of stillbirths, Intrauterine Demise [IUD] and miscarriages). This was obtained from West Midlands Fetal Medicine Centre, Birmingham Women’s Hospital, UK. The proportion of cases that fell into each category was multiplied by the unit cost for each weeks of gestation category. This derived an aggregated value of approximately £730. |
| **Vaginal Delivery, Elective Caesarean and Emergency Caesarean** | Vaginal Delivery and elective caesarean costs were £1775, indicating delivery without complications. The cost of emergency caesarean was £2582, as it was assumed that complications were encountered.                                                                                                                                                                          |
| **Follow-up**                           | The unit cost for follow-up was £646, which assumed an hourly rate of £110 per hour for a specialist nurse (Band 6 cost for |
each hour of patient contact) and £137 per hour for a medical consultant.

The cost of post-partum care varied depending on the unit the baby was admitted to and the amount of time spent. The unit cost per day for Intensive Care, High Dependency, Special Care and Transitional Care was £1076, £862, £409 and £373, respectively. The proportion of cases requiring post-partum care, relative to the overall sample, was multiplied by the average cost for all units (with a trimmed mean of 10%). An aggregate value of £2810 was derived.
Table S2. A2: Model Parameters

| Parameter                                      | Mean  | α   | n -α | Source          |
|------------------------------------------------|-------|-----|------|-----------------|
| **Combined Distribution***                     |       |     |      |                 |
| CMA Positive + ES Positive                     | 0.0120| 3   | 247  | Study Data      |
| CMA Positive + ES Negative                     | 0.0240| 6   | 244  | Study Data      |
| CMA Negative + ES Negative                     | 0.8640| 216 | 34   | Study Data      |
| CMA Negative + ES Positive                     | 0.1000| 25  | 225  | Study Data      |
| **Pregnancy outcome after positive CMA***       |       |     |      |                 |
| Termination of Pregnancy                       | 0.5556| 5   | 4    | Study Data      |
| Vaginal delivery                               | 0.0000| 0   | 9    | Study Data      |
| Emergency caesarean section                    | 0.1111| 1   | 8    | Study Data      |
| Elective caesarean section                     | 0.3333| 3   | 6    | Study Data      |
| **Pregnancy outcome after negative CMA***       |       |     |      |                 |
| Termination of Pregnancy                       | 0.3610| 87  | 154  | Study Data      |
| Vaginal delivery                               | 0.3942| 95  | 146  | Study Data      |
| Emergency caesarean section                    | 0.1162| 28  | 213  | Study Data      |
| Elective caesarean section                     | 0.1286| 31  | 210  | Study Data      |
| **Pregnancy outcome after positive ES***        |       |     |      |                 |
| Termination of Pregnancy                       | 0.5714| 16  | 12   | Study Data      |
| Vaginal delivery                               | 0.1786| 5   | 23   | Study Data      |
| Emergency caesarean section                    | 0.0714| 2   | 26   | Study Data      |
| Elective caesarean section                     | 0.1786| 5   | 23   | Study Data      |
| **Pregnancy outcome after negative ES***        |       |     |      |                 |
| Termination of Pregnancy                       | 0.3423| 76  | 146  | Study Data      |
| Vaginal delivery                               | 0.4054| 90  | 132  | Study Data      |
| Emergency caesarean section                    | 0.1216| 27  | 195  | Study Data      |
| Elective caesarean section                     | 0.1306| 29  | 193  | Study Data      |

A beta distribution is a family of continuous probability distributions defined on the interval [0,1], denoted by α and β, where α is the number of successes in a trial and β the number of failures.

*Dirichlet distribution is a multivariate generalisation of beta distribution

CC: Complete Cases Only (Analysis two) | CMA: Chromosomal Microarray | ES: Exome Sequencing
### Table S3. *Phenotype Single*: Model Parameters

| Parameter | Combined Distribution* | Mean | α | n-α | Source     |
|-----------|-------------------------|------|---|-----|------------|
| CMA Positive + ES Positive | 0.0103 | 2   | 192 | Study Data |
| CMA Negative + ES Positive | 0.0619 | 12  | 182 | Study Data |
| CMA Negative + ES Negative | 0.8969 | 174 | 20  | Study Data |
| CMA Positive + ES Negative | 0.0309 | 6   | 188 | Study Data |

**Pregnancy outcome after positive CMA***

| Event                               | Mean | α | n-α | Source     |
|-------------------------------------|------|---|-----|------------|
| Termination of Pregnancy            | 0.5000 | 4 | 4   | Study Data |
| Vaginal delivery                    | 0.0000 | 0 | 8   | Study Data |
| Emergency caesarean section         | 0.1250 | 1 | 7   | Study Data |
| Elective caesarean section          | 0.3750 | 3 | 5   | Study Data |

**Pregnancy outcome after negative CMA***

| Event                               | Mean | α | n-α | Source     |
|-------------------------------------|------|---|-----|------------|
| Termination of Pregnancy            | 0.3333 | 62| 124 | Study Data |
| Vaginal delivery                    | 0.4247 | 79| 107 | Study Data |
| Emergency caesarean section         | 0.1183 | 22| 164 | Study Data |
| Elective caesarean section          | 0.1237 | 23| 163 | Study Data |

**Pregnancy outcome after positive ES***

| Event                               | Mean | α | n-α | Source     |
|-------------------------------------|------|---|-----|------------|
| Termination of Pregnancy            | 0.6429 | 9 | 5   | Study Data |
| Vaginal delivery                    | 0.1429 | 2 | 12  | Study Data |
| Emergency caesarean section         | 0.0000 | 0 | 14  | Study Data |
| Elective caesarean section          | 0.2143 | 3 | 11  | Study Data |

**Pregnancy outcome after negative ES***

| Event                               | Mean | α | n-α | Source     |
|-------------------------------------|------|---|-----|------------|
| Termination of Pregnancy            | 0.3167 | 57| 123 | Study Data |
| Vaginal delivery                    | 0.4278 | 77| 103 | Study Data |
| Emergency caesarean section         | 0.1278 | 23| 157 | Study Data |
| Elective caesarean section          | 0.1278 | 23| 157 | Study Data |

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## Table S4. Phenotype Multiple: Model Parameters

| Parameter | Mean  | \(\alpha\) | \(n-\alpha\) | Source       |
|-----------|-------|-------------|--------------|--------------|
| **Combined Distribution** |       |             |              |              |
| CMA Positive + ES Positive | 0.0192 | 1           | 51           | Study Data   |
| CMA Negative + ES Positive | 0.1346 | 7           | 45           | Study Data   |
| CMA Negative + ES Negative | 0.8077 | 42          | 10           | Study Data   |
| CMA Positive + ES Negative | 0.0385 | 2           | 50           | Study Data   |
| **Pregnancy outcome after positive CMA** |       |             |              |              |
| Termination of Pregnancy | 0.3333 | 1           | 2            | Study Data   |
| Vaginal delivery | 0.3333 | 1           | 2            | Study Data   |
| Emergency caesarean section | 0.0000 | 0           | 3            | Study Data   |
| Elective caesarean section | 0.3333 | 1           | 2            | Study Data   |
| **Pregnancy outcome after negative CMA** |       |             |              |              |
| Termination of Pregnancy | 0.5306 | 26          | 23           | Study Data   |
| Vaginal delivery | 0.2653 | 13          | 36           | Study Data   |
| Emergency caesarean section | 0.0612 | 3           | 46           | Study Data   |
| Elective caesarean section | 0.1429 | 7           | 42           | Study Data   |
| **Pregnancy outcome after positive ES** |       |             |              |              |
| Termination of Pregnancy | 0.6250 | 5           | 3            | Study Data   |
| Vaginal delivery | 0.0000 | 0           | 8            | Study Data   |
| Emergency caesarean section | 0.1250 | 1           | 7            | Study Data   |
| Elective caesarean section | 0.2500 | 2           | 6            | Study Data   |
| **Pregnancy outcome after negative ES** |       |             |              |              |
| Termination of Pregnancy | 0.5000 | 22          | 22           | Study Data   |
| Vaginal delivery | 0.3182 | 14          | 30           | Study Data   |
| Emergency caesarean section | 0.0455 | 2           | 42           | Study Data   |
| Elective caesarean section | 0.1364 | 6           | 38           | Study Data   |

A beta distribution is a family of continuous probability distributions defined on the interval \([0,1]\), denoted by \(\alpha\) and \(\beta\), where \(\alpha\) is the number of successes in a trial and \(\beta\) the number of failures. *Dirichlet distribution is a multivariate generalisation of beta distribution. CMA: Chromosomal Microarray | ES: Exome Sequencing*
## Table S5. Phenotype Skeletal/Limb/Spinal: Model Parameters

| Parameter                                      | Mean  | α   | n-α  | Source      |
|------------------------------------------------|-------|-----|------|-------------|
| **Combined Distribution***                    |       |     |      |             |
| CMA Positive + ES Positive                     | 0.0345| 1   | 28   | Study Data  |
| CMA Negative + ES Positive                     | 0.0690| 2   | 27   | Study Data  |
| CMA Negative + ES Negative                     | 0.8621| 25  | 4    | Study Data  |
| CMA Positive + ES Negative                     | 0.0345| 1   | 28   | Study Data  |
| **Pregnancy outcome after positive CMA***      |       |     |      |             |
| Termination of Pregnancy                       | 0.5000| 1   | 1    | Study Data  |
| Vaginal delivery                               | 0.0000| 0   | 2    | Study Data  |
| Emergency caesarean section                    | 0.0000| 0   | 2    | Study Data  |
| Elective caesarean section                     | 0.5000| 1   | 1    | Study Data  |
| **Pregnancy outcome after negative CMA***      |       |     |      |             |
| Termination of Pregnancy                       | 0.3333| 9   | 18   | Study Data  |
| Vaginal delivery                               | 0.3704| 10  | 17   | Study Data  |
| Emergency caesarean section                    | 0.0741| 2   | 25   | Study Data  |
| Elective caesarean section                     | 0.2222| 6   | 21   | Study Data  |
| **Pregnancy outcome after positive ES***       |       |     |      |             |
| Termination of Pregnancy                       | 1.0000| 3   | 0    | Study Data  |
| Vaginal delivery                               | 0.0000| 0   | 3    | Study Data  |
| Emergency caesarean section                    | 0.0000| 0   | 3    | Study Data  |
| Elective caesarean section                     | 0.0000| 0   | 3    | Study Data  |
| **Pregnancy outcome after negative ES***       |       |     |      |             |
| Termination of Pregnancy                       | 0.2692| 7   | 19   | Study Data  |
| Vaginal delivery                               | 0.3846| 10  | 16   | Study Data  |
| Emergency caesarean section                    | 0.0769| 2   | 24   | Study Data  |
| Elective caesarean section                     | 0.2692| 7   | 19   | Study Data  |

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Table S6. *Phenotype Cardiac*: Model Parameters

| Parameter                        | Mean   | α    | n-α  | Source      |
|----------------------------------|--------|------|------|-------------|
| **Combined Distribution***       |        |      |      |             |
| CMA Positive + ES Positive       | 0.0000 | 0    | 43   | Study Data  |
| CMA Negative + ES Positive       | 0.1163 | 5    | 38   | Study Data  |
| CMA Negative + ES Negative       | 0.8372 | 36   | 7    | Study Data  |
| CMA Positive + ES Negative       | 0.0465 | 2    | 41   | Study Data  |
| **Pregnancy outcome after positive CMA*** |        |      |      |             |
| Termination of Pregnancy         | 0.0000 | 0    | 2    | Study Data  |
| Vaginal delivery                 | 0.0000 | 0    | 2    | Study Data  |
| Emergency caesarean section      | 1.0000 | 2    | 0    | Study Data  |
| Elective caesarean section       | 0.0000 | 0    | 2    | Study Data  |
| **Pregnancy outcome after negative CMA*** |        |      |      |             |
| Termination of Pregnancy         | 0.3659 | 15   | 26   | Study Data  |
| Vaginal delivery                 | 0.3659 | 15   | 26   | Study Data  |
| Emergency caesarean section      | 0.0976 | 4    | 37   | Study Data  |
| Elective caesarean section       | 0.1707 | 7    | 34   | Study Data  |
| **Pregnancy outcome after positive ES*** |        |      |      |             |
| Termination of Pregnancy         | 0.0000 | 0    | 5    | Study Data  |
| Vaginal delivery                 | 0.4000 | 2    | 3    | Study Data  |
| Emergency caesarean section      | 0.0000 | 0    | 5    | Study Data  |
| Elective caesarean section       | 0.6000 | 3    | 2    | Study Data  |
| **Pregnancy outcome after negative ES*** |        |      |      |             |
| Termination of Pregnancy         | 0.3947 | 15   | 23   | Study Data  |
| Vaginal delivery                 | 0.3421 | 13   | 25   | Study Data  |
| Emergency caesarean section      | 0.1053 | 4    | 34   | Study Data  |
| Elective caesarean section       | 0.1579 | 6    | 32   | Study Data  |

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| Parameter | Mean | α | n-α | Source          |
|-----------|------|---|-----|----------------|
| **Combined Distribution*** |      |   |     |                |
| CMA Positive + ES Positive | 0.0000 | 0 | 19  | Study Data     |
| CMA Negative + ES Positive | 0.0526 | 1 | 18  | Study Data     |
| CMA Negative + ES Negative | 0.8421 | 16| 3   | Study Data     |
| CMA Positive + ES Negative | 0.1053 | 2 | 17  | Study Data     |
| **Pregnancy outcome after positive CMA*** |      |   |     |                |
| Termination of Pregnancy | 0.5000 | 1 | 1   | Study Data     |
| Vaginal delivery | 0.0000 | 0 | 2   | Study Data     |
| Emergency caesarean section | 0.5000 | 1 | 1   | Study Data     |
| Elective caesarean section | 0.0000 | 0 | 2   | Study Data     |
| **Pregnancy outcome after negative CMA*** |      |   |     |                |
| Termination of Pregnancy | 0.5294 | 9 | 8   | Study Data     |
| Vaginal delivery | 0.2941 | 5 | 12  | Study Data     |
| Emergency caesarean section | 0.1176 | 2 | 15  | Study Data     |
| Elective caesarean section | 0.0588 | 1 | 16  | Study Data     |
| **Pregnancy outcome after positive ES*** |      |   |     |                |
| Termination of Pregnancy | 1.0000 | 1 | 0   | Study Data     |
| Vaginal delivery | 0.0000 | 0 | 1   | Study Data     |
| Emergency caesarean section | 0.0000 | 0 | 1   | Study Data     |
| Elective caesarean section | 0.0000 | 0 | 1   | Study Data     |
| **Pregnancy outcome after negative ES*** |      |   |     |                |
| Termination of Pregnancy | 0.5000 | 9 | 9   | Study Data     |
| Vaginal delivery | 0.2778 | 5 | 13  | Study Data     |
| Emergency caesarean section | 0.1667 | 3 | 15  | Study Data     |
| Elective caesarean section | 0.0556 | 1 | 17  | Study Data     |

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Table S8. Phenotype Nuchal Translucency: Model Parameters

| Parameter                              | Mean   | α    | n-α  | Source       |
|----------------------------------------|--------|------|------|--------------|
| **Combined Distribution***             |        |      |      |              |
| CMA Positive + ES Positive             | 0.0000 | 0    | 45   | Study Data   |
| CMA Negative + ES Positive             | 0.0889 | 4    | 41   | Study Data   |
| CMA Negative + ES Negative             | 0.8889 | 40   | 5    | Study Data   |
| CMA Positive + ES Negative             | 0.0222 | 1    | 44   | Study Data   |
| **Pregnancy outcome after positive CMA*** |    |      |      |              |
| Termination of Pregnancy               | 1.0000 | 1    | 0    | Study Data   |
| Vaginal delivery                       | 0.0000 | 0    | 1    | Study Data   |
| Emergency caesarean section            | 0.0000 | 0    | 1    | Study Data   |
| Elective caesarean section             | 0.0000 | 0    | 1    | Study Data   |
| **Pregnancy outcome after negative CMA*** |    |      |      |              |
| Termination of Pregnancy               | 0.2045 | 9    | 35   | Study Data   |
| Vaginal delivery                       | 0.5909 | 26   | 18   | Study Data   |
| Emergency caesarean section            | 0.1136 | 5    | 39   | Study Data   |
| Elective caesarean section             | 0.0909 | 4    | 40   | Study Data   |
| **Pregnancy outcome after positive ES*** |    |      |      |              |
| Termination of Pregnancy               | 1.0000 | 4    | 0    | Study Data   |
| Vaginal delivery                       | 0.0000 | 0    | 4    | Study Data   |
| Emergency caesarean section            | 0.0000 | 0    | 4    | Study Data   |
| Elective caesarean section             | 0.0000 | 0    | 4    | Study Data   |
| **Pregnancy outcome after negative ES*** |    |      |      |              |
| Termination of Pregnancy               | 0.1463 | 6    | 35   | Study Data   |
| Vaginal delivery                       | 0.6341 | 26   | 15   | Study Data   |
| Emergency caesarean section            | 0.1220 | 5    | 36   | Study Data   |
| Elective caesarean section             | 0.0976 | 4    | 37   | Study Data   |

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Table S9. *Phenotype Brain:* Model Parameters

| Parameter | Mean  | α   | n-α | Source     |
|-----------|-------|-----|-----|------------|
| **Combined Distribution*** |       |     |     |            |
| CMA Positive + ES Positive  | 0.0385 | 1   | 25  | Study Data |
| CMA Negative + ES Positive  | 0.0000 | 0   | 26  | Study Data |
| CMA Negative + ES Negative  | 0.9615 | 25  | 1   | Study Data |
| CMA Positive + ES Negative  | 0.0000 | 0   | 26  | Study Data |
| **Pregnancy outcome after positive CMA*** |       |     |     |            |
| Termination of Pregnancy    | 1.0000 | 1   | 0   | Study Data |
| Vaginal delivery            | 0.0000 | 0   | 1   | Study Data |
| Emergency caesarean section | 0.0000 | 0   | 1   | Study Data |
| Elective caesarean section  | 0.0000 | 0   | 1   | Study Data |
| **Pregnancy outcome after negative CMA*** |       |     |     |            |
| Termination of Pregnancy    | 0.5600 | 14  | 11  | Study Data |
| Vaginal delivery            | 0.1200 | 3   | 22  | Study Data |
| Emergency caesarean section | 0.1600 | 4   | 21  | Study Data |
| Elective caesarean section  | 0.1600 | 4   | 21  | Study Data |
| **Pregnancy outcome after positive ES*** |       |     |     |            |
| Termination of Pregnancy    | 1.0000 | 1   | 0   | Study Data |
| Vaginal delivery            | 0.0000 | 0   | 1   | Study Data |
| Emergency caesarean section | 0.0000 | 0   | 1   | Study Data |
| Elective caesarean section  | 0.0000 | 0   | 1   | Study Data |
| **Pregnancy outcome after negative ES*** |       |     |     |            |
| Termination of Pregnancy    | 0.5600 | 14  | 11  | Study Data |
| Vaginal delivery            | 0.1200 | 3   | 22  | Study Data |
| Emergency caesarean section | 0.1600 | 4   | 21  | Study Data |
| Elective caesarean section  | 0.1600 | 4   | 21  | Study Data |

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Table S10. Order of Dominance, A1

| Strategy                          | Cost (£) | Effectiveness | ICER |
|-----------------------------------|----------|---------------|------|
|                                   | Mean     | Incremental   | Mean | Incremental |       |
| Base case                         |          |               |      |             |      |
| CMA alone (Strategy One)          | 3654     | 0             | 0.0369 | 0.0000 | 0    |
| WES alone (Strategy Two)          | 5446     | 1792          | 0.0940 | 0.0570 | 31410|
| CMA then WES (Strategy Three)     | 5723     | 277           | 0.1208 | 0.0268 | 10307|
| CMA and WES (Strategy Four)       | 5800     | 78            | 0.1208 | 0.0000 | 0    |
| Scenario 1                        |          |               |      |             |      |
| CMA alone (Strategy One)          | 3654     | 0             | 0.0369 | 0.0000 | 0    |
| WES alone (Strategy Two)          | 5236     | 1582          | 0.0940 | 0.0570 | 27729|
| CMA then WES (Strategy Three)     | 5520     | 284           | 0.1208 | 0.0268 | 10596|
| CMA and WES (Strategy Four)       | 5590     | 70            | 0.1208 | 0.0000 | 0    |
| Scenario 2                        |          |               |      |             |      |
| CMA alone (Strategy One)          | 3654     | 0             | 0.0369 | 0.0000 | 0    |
| WES alone (Strategy Two)          | 5026     | 1372          | 0.0940 | 0.0570 | 24048|
| CMA then WES (Strategy Three)     | 5318     | 292           | 0.1208 | 0.0268 | 10885|
| CMA and WES (Strategy Four)       | 5380     | 62            | 0.1208 | 0.0000 | 0    |
| Scenario 3                        |          |               |      |             |      |
| CMA alone (Strategy One)          | 3654     | 0             | 0.0369 | 0.0000 | 0    |
| WES alone (Strategy Two)          | 4816     | 1162          | 0.0940 | 0.0570 | 20367|
| CMA then WES (Strategy Three)     | 5116     | 300           | 0.1208 | 0.0268 | 11174|
| CMA and WES (Strategy Four)       | 5170     | 54            | 0.1208 | 0.0000 | 0    |
| Scenario 4                        |          |               |      |             |      |
| CMA alone (Strategy One)          | 3654     | 0             | 0.0369 | 0.0000 | 0    |
| WES alone (Strategy Two)          | 4606     | 952           | 0.0940 | 0.0570 | 16685|
| CMA then WES (Strategy Three)     | 4914     | 308           | 0.1208 | 0.0268 | 11462|
| CMA and WES (Strategy Four)       | 4960     | 47            | 0.1208 | 0.0000 | 0    |
| Scenario 5                        |          |               |      |             |      |
| CMA alone (Strategy One)          | 3654     | 0             | 0.0369 | 0.0000 | 0    |
| WES alone (Strategy Two)          | 4396     | 742           | 0.0940 | 0.0570 | 13004|
| CMA then WES (Strategy Three)     | 4711     | 315           | 0.1208 | 0.0268 | 11751|
| CMA and WES (Strategy Four)       | 4750     | 39            | 0.1208 | 0.0000 | 0    |

Base case: Assume WES is £2100
Scenario 1: Assume WES has decreased by 10% and is therefore £1890
Scenario 2: Assume WES has decreased by 20% and is therefore £1680
Scenario 3: Assume WES has decreased by 30% and is therefore £1470
Scenario 4: Assume WES has decreased by 40% and is therefore £1260
Scenario 5: Assume WES has decreased by 50% and is therefore £1050

CMA: Chromosomal Microarray | ES: Exome Sequencing
Table S1. A2 Analysis Results

| Measure                  | Results                                                                                                                                                                                                 |
|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Detection Rates          | Table S12-S13 presents the findings for A2. Briefly, 13.60% of all cases were identified to have an anomaly. CMA alone identified approximately 26% of all possible cases and ES alone identified approximately 82% of all possible cases. The stepwise and the combined strategies identified all possible cases. |
| Incremental Cost Effectiveness Ratio (ICER) | The findings presented in Table S12-S13 show that compared to the cost of CMA, ES alone was found to be the least costly strategy. Even so, the stepwise was able to identify all of the possible anomalies at an incremental cost of £266 (€305/$341), when compared to ES alone. The ICER derived for the stepwise is therefore lower than the ICER derived for ES alone. This implies that it is more cost-effective to employ the stepwise, as opposed to ES alone, in order to identify an additional genetic diagnosis. In this case, the dominant strategy is the stepwise. This can be seen graphically in Figure S3. |
| Deterministic Sensitivity Analysis | In the limited deterministic sensitivity analysis (DSA), five additional scenarios were investigated following the base case analysis in A2 (Table S12-S13). Each scenario tested a reduction in the cost of ES of up to 50% by 10% decrements. The pattern of dominance remained consistent with the base case analysis in all but one scenario. When the cost of ES was reduced by 50% (∣£1050[€1,203/$1,347]), the pattern of dominance changes, such that ES was no longer a dominated strategy. This is clear, as the ICER for ES alone is lower than the ICER for the stepwise. This therefore implies that, based on the values of the ICER’s, ES alone can be considered as a suitable
strategy. However, if the WTP threshold exceeds £10581 (€12127/ $13,572), the stepwise will still remain the preferred strategy. This is because the stepwise yields more, in terms of effectiveness.

| Incremental Cost Effectiveness Curves |
|---------------------------------------|
| The PSA was undertaken to obtain the differences in the costs and effectiveness between each strategy in order to produce an incremental cost-effectiveness plane. Figure S5 shows the mean incremental costs and incremental effectiveness between CMA alone and ES alone for A2. The graph shows a large amount of parameter uncertainty, as the mean incremental costs and incremental effectiveness falls in the north east and the north-west quadrant of the plane. This indicates that ES is certain to be more costly than CMA, but there is a small probability, consistent with the data available, that ES is also less effective than CMA. Figure S6 shows the mean incremental costs and incremental effectiveness between CMA alone and the stepwise. The graph shows some parameter uncertainty, although all points fall within the north east region of the plane. This implies that in all cases the stepwise will identify more abnormalities than CMA alone, but at an additional cost. Figure S7 shows the mean incremental costs and incremental effectiveness between ES alone and the stepwise. There is a large amount of parameter uncertainty despite all points falling within the north east region of the plane. This implies that in all cases the stepwise will identify more abnormalities than ES alone, but at an additional cost. |

| Cost Effectiveness Acceptability |
|----------------------------------|
| Figure S8 presents the CEAC for A2, when the cost of ES is (€2,407/$2,694). At a WTP of £20,000 (€22,923/$25,654) the probability that the stepwise is cost-effective is approximately 36% and the probability that CMA alone is cost-effective is 56%. At a WTP of |
Curve (CEAC) £30,000 (€34,385/$38,481) the probability that the stepwise cost-effective is 90% and the probability that CMA alone is cost-effective is 6%.

Figure S9 presents the CEAC for A2, when the cost of ES is £1,050 (€1,203/$1,347). At a WTP of £20,000 (€22,923/$25,654) the probability that the stepwise is cost-effective is approximately 79% and the probability that CMA alone is cost-effective is less than 1%. At a WTP of £30,000 (€34,385/$38,481) the probability that the stepwise cost-effective is 94% and the probability that CMA alone is cost-effective is 0%. 
| Strategy                                      | Cost (£) | Effectiveness | ICER  |
|----------------------------------------------|----------|---------------|-------|
| **Base case**                                |          |               |       |
| CMA alone (Strategy One)                     | 3618     | 0.0360        |       |
| ES alone (Strategy Two)                      | 5422     | 1804 0.1120   | 23738 |
| CMA then ES (Strategy Three)                 | 5688     | 2070 0.1360   | 20703 |
| CMA and ES (Strategy Four)                   | 5764     | 2146 0.1360   | 21459 |
| **Scenario 1**                               |          |               |       |
| CMA alone (Strategy One)                     | 3618     | 0.0360        |       |
| ES alone (Strategy Two)                      | 5212     | 1594 0.1120   | 20975 |
| CMA then ES (Strategy Three)                 | 5486     | 1868 0.1360   | 18678 |
| CMA and ES (Strategy Four)                   | 5554     | 1936 0.1360   | 19359 |
| **Scenario 2**                               |          |               |       |
| CMA alone (Strategy One)                     | 3618     | 0.0360        |       |
| ES alone (Strategy Two)                      | 5002     | 1384 0.1120   | 18212 |
| CMA then ES (Strategy Three)                 | 5283     | 1665 0.1360   | 16654 |
| CMA and ES (Strategy Four)                   | 5344     | 1726 0.1360   | 17259 |
| **Scenario 3**                               |          |               |       |
| CMA alone (Strategy One)                     | 3618     | 0.0360        |       |
| ES alone (Strategy Two)                      | 4792     | 1174 0.1120   | 15449 |
| CMA then ES (Strategy Three)                 | 5081     | 1463 0.1360   | 14630 |
| CMA and ES (Strategy Four)                   | 5134     | 1516 0.1360   | 15159 |
| **Scenario 4**                               |          |               |       |
| CMA alone (Strategy One)                     | 3618     | 0.0360        |       |
| ES alone (Strategy Two)                      | 4582     | 964 0.1120    | 12685 |
| CMA then ES (Strategy Three)                 | 4879     | 1261 0.1360   | 12605 |
| CMA and ES (Strategy Four)                   | 4924     | 1306 0.1360   | 13059 |
| **Scenario 5**                               |          |               |       |
| CMA alone (Strategy One)                     | 3618     | 0.0360        |       |
| ES alone (Strategy Two)                      | 4372     | 754 0.1120    | 9922  |
| CMA then ES (Strategy Three)                 | 4676     | 1058 0.1360   | 10581 |
| CMA and ES (Strategy Four)                   | 4714     | 1096 0.1360   | 10959 |

Base case: Assume ES is £2100
Scenario 1: Assume ES has decreased by 10% and is therefore £1890
Scenario 2: Assume ES has decreased by 20% and is therefore £1680
Scenario 3: Assume ES has decreased by 30% and is therefore £1470
Scenario 4: Assume ES has decreased by 40% and is therefore £1260
Scenario 5: Assume ES has decreased by 50% and is therefore £1050

CMA: Chromosomal Microarray | ES: Exome Sequencing
| Strategy                        | Cost (£) | Effectiveness | ICER  |
|--------------------------------|----------|---------------|-------|
|                                | Mean     | Incremental   | Mean  | Incremental |       |
| **Base case**                  |          |               |       |             |       |
| CMA alone (Strategy One)       | 3618     | 0             | 0.0360| 0.0000      | 0     |
| WES alone (Strategy Two)       | 5422     | 1804          | 0.1120| 0.0760      | 23738 |
| CMA then WES (Strategy Three)  | 5688     | 266           | 0.1360| 0.0240      | 11091 |
| CMA and WES (Strategy Four)    | 5764     | 76            | 0.1360| 0.0000      | 0     |
| **Scenario 1**                 |          |               |       |             |       |
| CMA alone (Strategy One)       | 3618     | 0             | 0.0360| 0.0000      | 0     |
| WES alone (Strategy Two)       | 5212     | 1594          | 0.1120| 0.0760      | 20975 |
| CMA then WES (Strategy Three)  | 5486     | 274           | 0.1360| 0.0240      | 11406 |
| CMA and WES (Strategy Four)    | 5554     | 68            | 0.1360| 0.0000      | 0     |
| **Scenario 2**                 |          |               |       |             |       |
| CMA alone (Strategy One)       | 3618     | 0             | 0.0360| 0.0000      | 0     |
| WES alone (Strategy Two)       | 5002     | 1384          | 0.1120| 0.0760      | 18212 |
| CMA then WES (Strategy Three)  | 5283     | 281           | 0.1360| 0.0240      | 11721 |
| CMA and WES (Strategy Four)    | 5344     | 60            | 0.1360| 0.0000      | 0     |
| **Scenario 3**                 |          |               |       |             |       |
| CMA alone (Strategy One)       | 3618     | 0             | 0.0360| 0.0000      | 0     |
| WES alone (Strategy Two)       | 4792     | 1174          | 0.1120| 0.0760      | 15449 |
| CMA then WES (Strategy Three)  | 5081     | 289           | 0.1360| 0.0240      | 12036 |
| CMA and WES (Strategy Four)    | 5134     | 53            | 0.1360| 0.0000      | 0     |
| **Scenario 4**                 |          |               |       |             |       |
| CMA alone (Strategy One)       | 3618     | 0             | 0.0360| 0.0000      | 0     |
| WES alone (Strategy Two)       | 4582     | 964           | 0.1120| 0.0760      | 12685 |
| CMA then WES (Strategy Three)  | 4879     | 296           | 0.1360| 0.0240      | 12351 |
| CMA and WES (Strategy Four)    | 4924     | 45            | 0.1360| 0.0000      | 0     |
| **Scenario 5**                 |          |               |       |             |       |
| CMA alone (Strategy One)       | 3618     | 0             | 0.0360| 0.0000      | 0     |
| WES alone (Strategy Two)       | 4372     | 754           | 0.1120| 0.0760      | 9922  |
| CMA then WES (Strategy Three)  | 4676     | 304           | 0.1360| 0.0240      | 12666 |
| CMA and WES (Strategy Four)    | 4714     | 38            | 0.1360| 0.0000      | 0     |

Base case: Assume WES is £2100
Scenario 1: Assume WES has decreased by 10% and is therefore £1890
Scenario 2: Assume WES has decreased by 20% and is therefore £1680
Scenario 3: Assume WES has decreased by 30% and is therefore £1470
Scenario 4: Assume WES has decreased by 40% and is therefore £1260
Scenario 5: Assume WES has decreased by 50% and is therefore £1050

*CMA: Chromosomal Microarray | ES: Exome Sequencing*
Table S14. Sub-group analyses

| Strategy                        | Cost (£) | Effectiveness |
|--------------------------------|----------|---------------|
|                                | Mean     | Incremental   |
|                                | Mean     | Incremental   | ICER     |
| **Phenotype: Multiple Anomalies** |          |               |          |
| CMA alone (Strategy One)       | 3659     | 0.0577        |          |
| ES alone (Strategy Two)        | 5428     | 1769          | 0.1538   | 0.0962   | 18399   |
| CMA then ES (Strategy Three)   | 5668     | 2008          | 0.1923   | 0.1346   | 14920   |
| CMA and ES (Strategy Four)     | 5789     | 2130          | 0.1923   | 0.1346   | 15820   |
| **Phenotype: Single Anomaly**  |          |               |          |
| CMA alone (Strategy One)       | 3655     | 0.0412        |          |
| ES alone (Strategy Two)        | 5452     | 1797          | 0.0722   | 0.0309   | 58111   |
| CMA then ES (Strategy Three)   | 5721     | 2066          | 0.1031   | 0.0619   | 33395   |
| CMA and ES (Strategy Four)     | 5807     | 2152          | 0.1031   | 0.0619   | 34795   |
| **Phenotype: Skeletal/Limb/Spinal** |        |               |          |
| CMA alone (Strategy One)       | 3662     | 0.0690        |          |
| ES alone (Strategy Two)        | 5443     | 1781          | 0.1034   | 0.0345   | 51657   |
| CMA then ES (Strategy Three)   | 5665     | 2003          | 0.1379   | 0.0690   | 29048   |
| CMA and ES (Strategy Four)     | 5810     | 2148          | 0.1379   | 0.0690   | 31148   |
| **Phenotype: Cardiac**         |          |               |          |
| CMA alone (Strategy One)       | 3656     | 0.0465        |          |
| ES alone (Strategy Two)        | 5439     | 1783          | 0.1163   | 0.0698   | 25555   |
| CMA then ES (Strategy Three)   | 5695     | 2038          | 0.1628   | 0.1163   | 17528   |
| CMA and ES (Strategy Four)     | 5792     | 2136          | 0.1628   | 0.1163   | 18368   |
| **Phenotype: Abdominal/Gastro**|          |               |          |
| CMA alone (Strategy One)       | 3671     | 0.1053        |          |
| Strategy                  | Sample Size | Pheno Size | Pheno Rate | Exome Rate | Cost   |
|--------------------------|-------------|------------|------------|------------|--------|
| ES alone (Strategy Two)  | 5458        | 1787       | 0.0526     | -0.0526    | -33961 |
| CMA then ES (Strategy Three) | 5600       | 1929       | 0.1579     | 0.0526     | 36655  |
| CMA and ES (Strategy Four) | 5821       | 2150       | 0.1579     | 0.0526     | 40855  |
| Phenotype: Nuchal Translucency |            |            |            |            |        |
| CMA alone (Strategy One) | 3650        |            | 0.0222     |            |        |
| ES alone (Strategy Two)  | 5447        | 1797       | 0.0889     | 0.0667     | 26954  |
| CMA then ES (Strategy Three) | 5749       | 2099       | 0.1111     | 0.0889     | 23614  |
| CMA and ES (Strategy Four) | 5796       | 2146       | 0.1111     | 0.0889     | 24139  |
| Phenotype: Brain         |            |            |            |            |        |
| CMA alone (Strategy One) | 3654        |            | 0.0385     |            |        |
| ES alone (Strategy Two)  | 5462        | 1808       | 0.0385     | 0.0000     | (undefined) |
| CMA then ES (Strategy Three) | 5744       | 2090       | 0.0385     | 0.0000     | (undefined) |
| CMA and ES (Strategy Four) | 5825       | 2171       | 0.0385     | 0.0000     | (undefined) |

*CMA: Chromosomal Microarray | ES: Exome Sequencing*
Table S15. *Sub-group Analysis Results*

| Measure             | Results                                                                                                                                                                                                 |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Detection Rates     | The detection rates varied between strategies and subgroups (see Table S14). CMA detected between 2-10% of all phenotypes identified using USS. ES alone detected between 3-15% of all phenotypes identified using USS. The stepwise and the combined detected between 3-19% of all phenotypes identified using USS. It should be noted that all test strategies had a detection rate of approximately 3% for the brain subgroup. This is because both CMA and ES identified the same positive cases within the sample. |
| Incremental Cost    | Table S14 presents the ICER’s for each subgroup. The ICER for ES alone and the combined approach exceeded the stepwise for all subgroups but the Brain. This means that compared to CMA, the stepwise is the dominant strategy. The results suggest that if the WTP is at least £36,900 (€42,290/$47,330), the stepwise will be the preferred option for all subgroups. |
| Incremental Effectiveness Ratio (ICER) | The findings associated to the Brain subgroup show the ICER’s to be undefined. This is because there was no additional effectiveness per strategy, only additional costs. The findings therefore suggest that CMA will remain as the preferred strategy should the USS be indicative of an anomaly associated with the Brain, as CMA absolutely dominates all other strategies. Even so, the sample size for this subgroup was only 26. This might have been too small to show a true depiction of the cost-effectiveness of detecting an anomaly associated with the Brain. The ICER’s of each subgroup differed, meaning the necessary WTP for a strategy to be cost-effective varied. This was due to the different incremental costs and incremental effectiveness for each subgroup. It might therefore be more cost-effective to undertake the stepwise on... |
selected subgroups, where the incremental costs are lower and the effectiveness is significantly greater. For example, cases with multiple anomalies detected by USS will likely be preferred over cases with a single anomaly detected, as the incremental effectiveness is greater and the incremental costs are lower, which in turn, produces a lower ICER.

Furthermore, if the WTP threshold is £30,000 (€34,385/$38,481), based on the ICERS alone, employing the stepwise would not be recommended if a single anomaly, abdominal, gastro, or brain related anomaly is identified by USS. This is because the ICER’s for these sub-groups exceed the maximum threshold.

| Cost Effectiveness Acceptability Curve (CEAC) |
|-----------------------------------------------|
| A PSA was undertaken to examine the level of uncertainty surrounding the parameters used for each phenotype subgroup. The PSA enabled the model to derive a CEAC for each group, which states the probability each strategy will be cost-effective. |
| **Phenotype: Multiple Anomalies** |
| Figure S10 presents the CEAC for the multiple anomaly subgroup. The figure shows that at a WTP of £20,000 (€22,923/$25,654), the probability that CMA is cost-effective is 29% and the probability that the stepwise is cost-effective is 56%. At a WTP of £30,000 (€34,385/$38,481), Figure S10 illustrates that the probability that CMA is cost-effective is 7%, the probability that ES alone is cost-effective is 10%, and the probability that stepwise is cost-effective is 83%. |
| **Phenotype: Single Anomaly** |
| Figure S11 presents the CEAC for the multiple anomaly subgroup. The figure shows that at a WTP of £20,000 (€22,923/$25,654), the probability that CMA is cost-effective is 95%, whereas the probability that stepwise is cost-effective is 4%. At a WTP of £30,000 |
(€34,385/$38,481), the figure indicates that the probability that CMA is cost-effective is 64%, whereas the probability that stepwise is cost-effective is 35%. If the WTP is at least £35,000 (€40,115/$44,894), the probability that stepwise is cost-effective exceeds the probability that CMA is cost-effective. The findings suggest that the stepwise is likely to be more cost-effective when the USS is indicative of multiple anomalies compared to the single anomaly subgroup, as the probability is greater amongst the group. Nonetheless, the sample size of the multiple anomaly subgroup was much lower compared to the single anomaly subgroup. Therefore, the test results of the samples may have subsequently influenced the PSA findings.

*Phenotype: Skeletal/Limb/Spinal*

Figure S12 presents the CEAC for the subgroup associated with skeletal, limb and spinal anomalies. At a WTP of £20,000 (€22,923/$25,654) the probability that the stepwise is cost-effective is approximately 15% and the probability that CMA alone is cost-effective is 74%. At a WTP of £30,000 (€34,385/$38,481) the probability that the stepwise cost-effective is 32% and the probability that CMA alone is cost-effective is 56%. If the WTP is greater than £40,000 (€45,846 / $51,308), the probability that the stepwise is cost-effective will exceed the probability that CMA alone is cost-effective.

*Phenotype: Cardiac*

Figure S13 presents the CEAC for the subgroup associated with cardiac anomalies. At a WTP of £20,000 (€22,923/$25,654) the probability that the stepwise and CMA alone are cost-effective is approximately 45%. At a WTP of £30,000 (€34,385/$38,481) the
probability that the stepwise cost-effective is 76% and the probability that CMA alone is cost-effective is 17%. As the WTP increases, the probability that the stepwise is cost-effective becomes closer to 100%.

**Phenotype: Abdominal/Gastro**

Figure S14 presents the CEAC for the subgroup associated with abdominal and gastro anomalies. At a WTP of £20,000 (€22,923/$25,654) the probability that the stepwise is cost-effective is approximately 20% and the probability that CMA alone is cost-effective is 80%. At a WTP of £30,000 (€34,385/$38,481) the probability that the stepwise cost-effective is 32% and the probability that CMA alone is cost-effective is 67%. If the WTP is greater than £50,000 (€57,308/ $64,135), the probability that the stepwise is cost-effective will exceed the probability that CMA alone is cost-effective.

**Phenotype: Nuchal Translucency**

Figure S15 presents the CEAC for the subgroup associated with nuchal translucency anomalies. At a WTP of £20,000 (€22,923/$25,654) the probability that the stepwise is cost-effective is 20% and the probability that CMA alone is cost-effective is 61%. At a WTP of £30,000 (€34,385/$38,481) the probability that the stepwise cost-effective is 40% and the probability that CMA alone is cost-effective is 35%.

**Phenotype: Brain**

Figure S16 presents the CEAC for the subgroup associated with brain anomalies. At a WTP of £20,000 (€22,923/$25,654) and £30,000 (€34,385/$38,481), the probability that the stepwise is cost-effective is 0% and the probability that CMA alone is cost-effective is 100%. There is no threshold whereby the probability of cost-effectiveness changes. This is because the only difference between each strategy was the cost.
The decision tree was built for the purpose of the study. The branch structure for CMA (Chromosomal Microarray), ‘Normal Diagnosis’, follows the same structure as the ‘Abnormal Diagnosis’. That is, after the diagnosis has been defined by QF-PCR and USS, the individual moves to their CMA tests, which can be either positive or negative. The patient finally reaches their pregnancy outcome, which can be: 1. Termination of Pregnancy (TOP)/ Intrauterine Demise (IUD) 2. Elective Caesarean (C/S) 3. Emergency C/S 4. Vaginal Delivery. The same branch structure is been applied to Exome Sequencing (ES) alone.

The branch structure for the Stepwise, ‘Normal Diagnosis’, follows the same structure as the ‘Abnormal Diagnosis’. That is, after the diagnosis has been defined by QF-PCR and USS, the individual moves to their CMA tests, which can be either positive or negative. If the individual has a positive test result, no further tests are undertaken and the patient proceeds to their pregnancy outcome (TOP/IUD, Elective C/S, Emergency C/S; Vaginal Delivery). If a the CMA test result reads negative, the individual is required to undertake an ES test. The results of the ES test can be either positive of negative. In either case, once the result has been confirmed, the patient moves to their pregnancy outcome.
Figure S2. A1: Incremental Cost Effectiveness Plane: ES and Stepwise

Figure S3. A2: Cost Effectiveness Analysis, ES: £2,100
Figure S4. A2: Cost Effectiveness Analysis, ES: £1,050

![Cost Effectiveness Analysis Graph]

Figure S5. A2: Incremental Cost Effectiveness Plane: CMA and ES

![Incremental Cost Effectiveness Plane Graph]
Figure S6. A2: Incremental Cost Effectiveness Plane: CMA and Stepwise

Figure S7. A2: Incremental Cost Effectiveness Plane: ES and Stepwise
Figure S8. A2: Cost Effectiveness Acceptability Curve (ES: £2100)

Figure S9. A2: Cost Effectiveness Acceptability Curve (ES: £1050)
Figure S10. Cost Effectiveness Acceptability Curve for Multiple Anomalies (ES: £2,100)

Figure S11. Cost Effectiveness Acceptability Curve for Single Anomalies (ES: £2,100)
Figure S12. Cost Effectiveness Acceptability Curve for Skeletal, Limb and Spinal (ES: £2100)

Figure S13. Cost Effectiveness Acceptability Curve for Cardiac (ES: £2100)
Figure S14. Cost Effectiveness Acceptability Curve for Abdominal and Gastro (ES: £2100)

Figure S15. Cost Effectiveness Acceptability Curve for Nuchal Translucency (ES: £2100)
Figure S16. Cost Effectiveness Acceptability Curve for Brain (ES: £2100)