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Statistical Analysis Plan

Clinical Investigation Plan Title	A multi-center observational study during pregnancy for women with T1DM treated with the Paradigm insulin pumps donated by the 'Wielka Orkiestra Świątecznej Pomocy' Foundation in Poland
Clinical Investigation Plan Identifier	Poland Orchestra Study
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	*New Document*	[redacted]
2.0	*10. Statistical Appendices* *The following tables were added:* *Table Subject Disposition* *Table Subject Withdrawal Reason* *Table Subject Disposition and Center Specific Information* *Table Proportion of subjects achieving HbA1c < 6% , 6.5%, 7%, 7.5%, 8%* *Table HbA1c Change Summary* *Table Summary of Sensor Glucose (SG) Stratified by Enrollment Groups* *Table Summary of Sensor Glucose (SG) Stratified by Pregnancy Outcome* *Table Summary of Sensor Glucose (SG) Stratified by Pregnancy Completeness* *Table Summary of Sensor Glucose (SG) Stratified by Sensor Time* *Table Summary of Sensor Glucose (SG) Stratified by Pump Time* *Table Summary of Sensor Glucose (SG) Stratified by PregnancyTrimester* *Table Time Spend in Range (%) of Sensor Glucose (SG) Stratified by Sensor Time* *Table Time Spend in Range (%) of Sensor Glucose (SG) Stratified by Pump Time* *Table Time Spend in Range (%) of Sensor Glucose (SG) Stratified by Pregnancy Trimester* *Table Summary of Subject Mean AUC of Hypoglycemic Stratified by Sensor Time* *Table Summary of Subject Mean AUC of Hypoglycemic Stratified by Pump Time* *Table Summary of Subject Mean AUC of Hypoglycemic Stratified by Pregnancy Trimester* *Table Summary of Subject Mean AUC of Hyperglycemic Stratified by Sensor Time* *Table Summary of Subject Mean AUC of Hyperglycemic Stratified by Pump Time* *Table Summary of Subject Mean AUC of Hyperglycemic Stratified by Pregnancy Trimester* *Table Summary of SMBG Stratified by Enrollment Groups* *Table Summary of SMBG Stratified by Pregnancy Outcome* *Table Summary of SMBG Stratified by Completeness of Treatment Phase*	[redacted]

Version	Summary of Changes	Author(s)/Title
	Table Summary of SMBG Stratified by Pregnancy Trimester *Table Incidence Rates of Delivery Modes (Overall)* *Table Incidence Rates of Delivery Modes (Enrolled before planned pregnancy)* *Table Incidence Rates of Delivery Modes (Enrolled during pregnancy)* *Table Incidence Rates of Mscarriage and Perterm Delivery (Overall)* *Table Incidence Rates of Mscarriage and Perterm Delivery (Enrolled before planed pregnancy)* *Table Incidence Rates of Mscarriage and Perterm Delivery (Enrolled during pregnancy)* *Table Summary of Pregnancy Related Serious Adverse Events* *Table Summary of Large for Gestational Age (90th)* *Table BMI Summary (Subjects enrolled before planned pregnancy)* *Table BMI Summary (Subjects enrolled during pregnancy)* *Table Summary of Albumin/Creatinine Ratio (Subjects enrolled before planned pregnancy)* *Table Summary of Albumin/Creatinine Ratio (Subjects enrolled during pregnancy)* *Table Summary of Daily Insulin Requirements (units)* *Table Summary of Serious Adverse Events* *Table Summary of Serious Adverse Events and Type of medical attendance* *Section Questionnaire and Surveys was added* *Section Device Information at Delivery was added* *Some notes were added.* *The head of Table Delivery and Neonatal Data was revised* *The head of Table Delivery and Neonatal Data was revised* *Table Summary of Demographics and Baseline Characteristics was revised, summary of Insulin Regimen, Previous Severe Hypoglycemia and DKA History was added* *The following tables were deleted:* *Table Subject Disposition (Total)* *Table Subject Disposition (Enrolled before planned pregnancy)* *Table Subject Disposition (Enrolled before planned pregnancy)* *Table Subject Miscarriage (Total)* *Table Subject Miscarriage (Enrolled before planned pregnancy)* *Table Subject Miscarriage (Enrolled during pregnancy)* *Table Device Compliance* *Table Alerts Settings (Low Limit)* *Table Alerts Settings (High Limit)*	

Version	Summary of Changes	Author(s)/Title
	Table Device Data *Table LGS Events* *Table LGS Limit* *Table 2 Hour LGS Events (by Subject)* *Table 2 Hour LGS Events (Total)* *Table CareLink Account* *Table Delivery Time (Total)* *Table Delivery Time (Enrolled before planned pregnancy)* *Table Delivery Time (Enrolled during pregnancy)*	

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2. List of Abbreviations and Definitions of Terms

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Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AUC	Area under The Curve
A1c/A1C	Glycated/Glycosylated Hemoglobin
BP	Biostatistical Plan
CGM	Continuous Glucose Monitoring
CS	Caesarean Section
CIP	Clinical Investigation Plan
CRO	Contract Research Organization
DMC	Data Monitoring Committee
DTL	Delegated Tasks List
DTSQ	Diabetes Treatment Satisfaction Questionnaire
e-CRF	Electronic Case Report Form
EDC	Electronic Data Capture
FU	Follow up
HbA1c	Glycated/Glycosylated Hemoglobin
HFS	Hypoglycemia Fear Survey
HTA Consulting	Contracted CRO
ISF	Investigator Site File
MAGE	Mean Amplitude of Glucose Excursion
MDI	Multiple Daily Injections

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MEC	Medical Ethical Committee
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SG	Sensor Glucose (glucose concentration measured by the sensor)
SOP	Standard Operating Procedure

3. Introduction

Diabetic pregnancies are associated with considerable risks for both the woman and the fetus. Risks for the woman include miscarriage, hypoglycaemia, ketoacidosis, pre-eclampsia, premature labour, polyhydramnios and obstructed labour, with increased rates of instrumental delivery and caesarean section. Babies are at increased risk of congenital malformation and macrosomia with consequent increased rates of perinatal mortality, birth injuries, neonatal hypoglycaemia, jaundice and respiratory distress. [1– 9]

High-quality cohort studies have established the relation between glucose control before conception and the incidence of miscarriage and congenital malformations[10]. High HbA1c levels in early[1,2,4–8] and late[3] pregnancy are associated with these risks and complications. Congenital malformations and the risk of miscarriage increases as first-trimester HbA1c increases above the normal range, and evidence shows that hyperglycaemia during pregnancy are associated with fetal macrosomia (and associated birth injury and caesarean sections) and fetal morbidity.[10] A hyperglycaemic intrauterine environment, may also predispose the child to Type 2 diabetes or pre-diabetes[11,12] and to being overweight.[12]

Achieving tight glucose control throughout pregnancy is challenging. A UK study showed pregnancies treated with multiple daily injections (MDI) spend eight to ten hours per day with glucose levels above the recommended range[13] resulting in a 3-5 times greater rate of major congenital malformation, stillbirth and neonatal death than seen in the background maternity population[4,14]. For those pregnancies delivering "healthy" live born infants, 66% are delivered by caesarean section, 50% are large for gestational age, 37% are delivered preterm and 40% are admitted to neonatal intensive care[15]. Interestingly in Germany, where insulin pump therapy (CSII) use is common, pregnancy outcomes have improved in recent years with decreases in stillbirths, premature delivery and macrosomia,[16] which the authors relate to improved diabetic rather than obstetric care.

The strict glycaemic control needed to ameliorate the risk of complications is challenged factors such as undetected post-prandial hyperglycaemia and overnight hypoglycaemia[17] and an increased risk of severe hypoglycaemia[18]. Studies have shown that improvements in HbA1c are achieved but were associated with increases in hypoglycaemia[19,20].

Severe hypoglycaemia (SH), accompanied by unconsciousness, convulsions and hospitalization[21-23], is a feared condition among non-pregnant subjects with diabetes[24], and affects women in particular[25]. Yet SH

affects between 25-40% mothers[26] and is three to five times as frequent in early pregnancy as in the period prior to pregnancy[21,22]. Rates of SH in the late first and early second trimester showed an increase of 16%[27], and in an intensively treated group subjects had 15 times more SH then the conventionally treated group[28]. Nocturnal hypoglycaemia is also common in the first trimester, with a 37% prevalence shown by hourly venous sampling between 22:00h-07:00h[29]. Ironically, during pregnancy, hypoglycaemia is less harmful to the fetus than to the mother[30], but hyperglycaemia poses increased risks for the fetus. Therefore, from the perspective of fetal outcomes, strict metabolic control in early pregnancy must still be advocated, but other means for preventing severe hypoglycaemia should be implemented[31].

CSII in non-pregnant Type 1 subjects was associated with a reduced rate of severe hypoglycaemia without adversely affecting glycaemic control when compared with MDI therapy[30]. There is recent convincing evidence from multicenter randomised controlled trials (RCT) that both CSII and continuous glucose monitoring (CGM) independently, or in combination as sensor-augmented pump therapy (SAP) improve glycaemic control by decreasing HbA1c in the range of -0.43% to -1.2%[32-38]. An RCT of 71 pregnancies complicated with diabetes had an end-of-pregnancy improvement of -0.6% and reduced risk of macrosomia when using CGM[13].

Postprandial blood glucose levels have a stronger association with incidence of macrosomia than HbA1c. Two RCTs found that monitoring of post-prandial glucose levels produced better outcomes than pre-prandial monitoring[10]. Neonatal outcomes are more closely associated with hyperglycaemic excursions than with the average glycaemic control[39-41]. The frequency, magnitude and duration of hyperglycaemic excursions, are best captured by CGM[13] which has an accuracy comparable to gold standard plasma glucose measurements in pregnancy[41] yet provides continuous information on glucose levels. Indeed, analysis of CGM for hyperglycaemia may be a useful marker of anticipated neonatal outcomes[43].

The prevention of severe hypoglycaemia has been demonstrated with CGM-related features such as alarms[44], and automatic insulin suspension (LGS)[45,46]. The use of CGM reduced the incidence of SH by 32.8% in adults[47] and the LGS feature reduced SH by 46% in children[45] and 69% in a mixed population[46]. Inappropriate treatment of hypoglycaemia may result in hyperglycaemia, but when the LGS feature was triggered in response to hypoglycaemia, there was no rebound hyperglycaemia observed[48]. In addition to a decrease in SH events, CGM also reduces the time spent in the hypoglycaemia range[38,49,50,51] and effectively reduced the fear of hypoglycemia and the fear of severe hypoglycaemia[47].

In conclusion, the management of diabetes during pregnancy needs to ensure an appropriate HbA1c is attained before and during pregnancy while reducing the mothers' exposure to hypoglycaemia and severe hypoglycaemic events, and reducing the fetus' exposure to hyperglycaemia. Sensor-augmented pump therapy provides the technology to enable reductions of HbA1c, to anticipate and alert the mother to glucose levels outside the target range, and to assist in preventing severe-hypoglycaemic events without the risk of rebound hyperglycaemia.

In 2012, the Orchestra Foundation (Fundacja Wielka Orkiestra Świątecznej Pomocy) decided to fund Insulin Pump Therapy (CSII) for pregnant women in the pre-conception period, during pregnancy and six weeks after delivery in Poland. The foundation also covers sensor use for about 1/3 of the study participants during the pregnancy period (SAP – Sensor Augmented Pump). Orchestra has requested that a professional data collection is organized from the patients who benefit from this donation in all investigation sites that received the donated devices. Medtronic is engaged in creating the design of the

registry as well as in the data management that will allow publication of the results in a journal/journals to be selected by the Publication Committee.

4. Study Objectives

The aim of this study is to document the use of insulin pump therapy (CSII), including sensor augmented pump therapy (SAP), before, during and after pregnancy in women with Type 1 Diabetes Mellitus benefiting from the Orchestra donation of Paradigm REAL-Time and Paradigm Veo pumps in Poland.

Primary objectives:

To assess the benefits of CSII, includingSAP, on the maternal glycemic control (HbA1c and Continuous Glucose Monitoring data)

Secondary objectives:

- To assess the prevalence of pregnancy complications (rates of preterm delivery, infant birth weight, neonatal care admissions) from preconception phase, throughout pregnancy, during delivery and after delivery during lactation phase (up to 6 weeks)
- To report and assess the potential benefits of CSII, including SAP,on neonatal outcomes
- To evaluate change in patient-reported outcomes using the Hypoglycemia Fear Survey (HFS) and the Diabetes Treatment Satisfaction Questionnaire (DTSQs and DTSQc)

5. Investigation Plan

Study design:

The project is designed as a multi-center prospective observational Post-Market-Release study to be conducted in up to 30 centers in Poland.

Total duration of the study per patient will be up to 22 months (up to 12 months pre-conception phase, pregnancy, and 6 weeks after delivery). The optimal study start is the beginning of pre-conception phase, however, pregnant women up to the 16th week of pregnancy can participate in the study too. The study end is 6 weeks after delivery. If conception does not occur within 12-months, the patient's study participation is terminated, and the insulin pump might be taken away from the patient. The following therapy is decided by the investigator. If the pump is not taken away after the 12-month of trial period for conception, the patient can continue insulin pump therapy until the pump is needed for another patient.

The study started in May 2013; enrolment period is planned for 30 months which can be modified by the decision of the Steering Committee The final report will be available within 24 months after the end of enrolment.. Data collection will be stopped when data have been collected from 100 pregnancies with complete follow-up (including pre-conception phase, pregnancy, delivery and 6 weeks of lactation).

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Treatment

- Approximately 2/3 of the study subjects will be provided with the Paradigm REAL-Time (stand-alone pump therapy, CSII), and rest of the subjects will be provided with the Paradigm Veo, MiniLink transmitter and sensors (sensor augmented pump therapy - SAP). The decision about the type of treatment is made by the Health Care Professional (HCP) together with the patient independently of the study. It is advised to choose sensor augmented pump therapy for patients who present overall good compliance and ability to understand and use such a therapy, as assessed by the treating physician.
- MiniLinks and sensors are provided free of charge mainly to Paradigm Veo users, from the pre-conception period until one month after delivery, ideally with wearing the sensor during delivery. For all planned deliveries with the sensor-augmented Paradigm pumps, the sensor should be ideally started 2 to 3 days before the delivery.
- Patients on the sensor-augmented Paradigm pumps can get as many sensors free of charge as recommended by their HCPs.
- Patients on the Paradigm REAL-Time without free of charge MiniLinks donated by the Orchestra Foundation can use Continuous Glucose Monitoring (MiniLink and sensors) to their own desire and costs, if agreed with the HCP.
- Patients attend regular routine follow-up without special requirements, where medical information is being collected in the eCRF system and the data from devices (pumps and meters) is being uploaded into CareLink Clinical.
- Women with miscarriage can keep their pump for additional 3 months after the miscarriage, if they want to continue the therapy.

Study hypothesis:

There is no hypothesis testing for this study. Analysis results will be presented by summary/descriptive statistics. Detailed statistical analysis plan will be described in the separate Biostatistical Plan (BP).

Study population:

The study subject population is women with Type 1 Diabetes Mellitus at the age of 18-45 who

- plan pregnancy
- are in the early phase of pregnancy, up to the 16th week

Study Methods:

- **Point of enrollment**

The investigator will check beforehand if the patient would meet the inclusion and exclusion criteria, and then ask the patient, if she agrees to participate in the study. After signing and dating the PIC, the patient is considered enrolled in the study. When the investigator creates a new eCRF patient account, the system automatically generates a patient ID code. The patients' ID codes will be documented in the enrollment log.

- **Implant or procedure aspects**

Procedures:

Patient enrolled before planned pregnancy

Visit 1a

- Inform the patient about study goals and procedures
- Ask the patient to sign and date the Patient Informed Consent form
- Ask patient to complete the HFS and DTSQs questionnaires
- Create a patient account in eCRF, and document the patient's ID code in the enrollment log
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the eCRF
- Check if the patient is properly trained on the loaned devices like the insulin pump, BG meter and sensor (if applicable)
- Document basal rate setting on the insulin pump
- Check the Bolus Wizard setting like the carbohydrate ratio, insulin sensitivity, target range, and active insulin time (if applicable)
- Check if the patient uses the reservoir and the infusion set as required
- If the patient is treated with SAP or she wants to use the sensor during the study period, make sure the patient is instructed on how to use the Continuous Glucose Monitoring feature of the pump, how to insert the sensor, and how to use the MiniLink transmitter
- Check it patient is aware of product support, and if necessary, give her the product helpline telephone number
- Fill in the eCRF and submit the data
- Create a CareLink Clinical account, and upload the data from the insulin pump (and BG meter, if applicable)

If the patient is not properly trained, retraining is required. Then follow these training guidelines:

Patient training guidelines

Patients have to be properly trained on how to use the insulin pump and the consumables. Training is provided by the Health Care Professional (HCP) from the investigation site, or a Certified Product Trainer (CPT) based on the local practice. The trainer follows the standard training checklist during the training. When the training is completed, the checklist has to be signed by the patient and the trainer, and filed in the investigation site file.

Patients who are selected for insulin pump therapy only (without the sensor), receive the Paradigm REAL-Time 722 insulin pump. They are trained for the use of the insulin pump, and they do not have to be instructed on the CGM related features of the insulin pump, unless they intend to purchase and use sensors during the study period.

Patients who are selected for SAP (insulin pump and sensor), receive the Paradigm Veo 754 insulin pump. They have to be trained for all features of the insulin pump including the continuous glucose monitoring (CGM) features.

Product support, helpline

Patients have to be trained on how to do basic troubleshooting, and they have to receive the Product Support (Helpline) phone number from the trainer. In case of device related problems, they should contact the Helpline.

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Sponsor respresentatives may perform study activities such as providing technical support and programming support during follow up.

Back-up therapy

In case of device failure, the patient should be able to switch to back-up therapy until replacement device is provided. It is recommended to keep syringes, insulin pens and insulin cartridges on hand as back-up.

Pump start, pump settings

Guidelines on how to start a patient on the insulin pump will be provided to investigation sites, and this document will be kept separately from the CIP.

Visit 2a – visit during pregnancy: 12th week (± 4 weeks window)

- Weigh the patient
- Measure the patient's blood pressure
- SAP treatment: If the patient has not used the sensor during the preconception period, make sure the patient is instructed on how to use the Continuous Glucose Monitoring feature of the Paradigm Veo insulin pump, how to insert the sensor, and how to use the MiniLink transmitter
- Collect the patient's medical data listed in the relevant eCRF
- Make therapy adjustment, and change pump settings, if necessary
- Check infusion site, make sure patient uses infusion sets properly
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Visit 2b – no conception in 12 months (± 2 weeks window)

- Ask patient to complete the HFS and DSTQs questionnaires
- Weigh the patient
- Collect the patient's medical data listed in the relevant eCRF
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)
- Terminate pump therapy

Visit 3 – visit during pregnancy: 24th week (± 2 weeks window)

- Ask patient to complete the HFS, DSTQs and DSTQc questionnaires
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Make therapy adjustment, and change pump settings, if necessary
- Check infusion site, make sure patient uses infusion sets properly
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Visit 4 – visit during pregnancy: 36th week (± 2 weeks window)

- Ask patient to complete the HFS and DSTQs questionnaires

- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Make therapy adjustment, and change pump settings, if necessary
- Check infusion site, make sure patient uses infusion sets properly
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Visit 5 – optional visit after delivery (+ 2 weeks window)

- Weigh the patient before and after delivery
- Collect the delivery data listed in the relevant eCRF
- Collect the neonatal outcome data listed in the relevant eCRF
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Visit 6 – 6 weeks after delivery (± 2 weeks window)

- Ask patient to complete the HFS and DTSQs questionnaires
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)
- Terminate pump therapy

Miscarriage – any time

- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Discuss with patient if she wants to continue the same therapy (CSII or SAP)
- Check infusion site, make sure patient uses infusion sets properly (if applicable)
- Make therapy adjustment, and change pump settings, if necessary
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Early dropout – any time

- Ask patient to complete the HFS and DTSQs questionnaires, if patient agrees
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Discuss with patient if she wants to continue the same therapy (CSII or SAP)
- Check infusion site, make sure patient uses infusion sets properly (if applicable)
- Make therapy adjustment, and change pump settings, if necessary
- Fill in the eCRF and submit the data

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- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Patient enrolled during pregnancy, up to the 16th week

Visit 1b (up to 16th week of pregnancy)

- Inform the patient about study goals and procedures
- Ask the patient to sign and date the Patient Informed Consent form
- Ask patient to complete the HFS and DTSQs questionnaires
- Create a patient account in eCRF, and document the patient's ID code in the enrollment log
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the eCRF
- Check if the patient is properly trained on the loaned devices like the insulin pump, BG meter and sensor (if applicable)
- Document basal rate setting on the insulin pump
- Check the Bolus Wizard setting like the carbohydrate ratio, insulin sensitivity, target range, and active insulin time (if applicable)
- Check if the patient uses the reservoir and the infusion set as required
- If the patient is treated with SAP or she wants to use the sensor during the study period, make sure the patient is instructed on how to use the Continuous Glucose Monitoring feature of the pump, how to insert the sensor, and how to use the MiniLink transmitter
- Check if the patient is aware of product support, if necessary, give her the product helpline telephone number
- Fill in the eCRF and submit the data
- Create a CareLink Clinical account, and upload the data from the insulin pump (and BG meter, if applicable)

If the patient is not properly trained, retraining is required. Then follow these training guidelines:

Patient training guidelines

Patients have to be properly trained on how to use the insulin pump and the consumables. Training is provided by the Health Care Professional (HCP) from the investigation site, or a Certified Product Trainer (CPT) based on the local practice. The trainer follows the standard training checklist during the training. When the training is completed, the checklist has to be signed by the patient and the trainer, and filed in the investigation site file.

Patients who are selected for insulin pump therapy only (without the sensor), receive the Paradigm REAL-Time 722 insulin pump. They are trained for the use of the insulin pump, and they do not have to be instructed on the CGM related features of the insulin pump, unless they intend to purchase and use sensors during the study period.

Patients who are selected for SAP (insulin pump and sensor), receive the Paradigm Veo 754 insulin pump. They have to be trained for all features of the insulin pump including the continuous glucose monitoring (CGM) features.

Product support, helpline

Patients have to be trained for how to do basic troubleshooting, and they have to receive the Product Support (Helpline) phone number from the trainer. In case of device related problems, they should contact the Helpline.

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Sponsor respresentatives may perform study activities such as providing technical support and programming support during follow up.

Back-up therapy

In case of device failure, patient should be able to switch to back-up therapy until replacement device is provided. It is recommended to keep syringes, insulin pens and insulin cartridges on hand as back-up.

Pump start, pump settings

Guidelines on how to start a patient on the insulin pump will be provided to investigation sites, and this document will be kept separately from the CIP.

Visit 3 – visit during pregnancy: 24th week (± 2 weeks window)

- Ask patient to complete the HFS, DTSQs and DTSQc questionnaires
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Make therapy adjustment, and change pump settings, if necessary
- Check infusion site, make sure patient uses infusion sets properly
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Visit 4 – visit during pregnancy: 36th week (± 2 weeks window)

- Ask patient to complete the HFS and DTSQs questionnaires
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Make therapy adjustment, and change pump settings, if necessary
- Check infusion site, make sure patient uses infusion sets properly
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Visit 5 – optional visit after delivery (+ 2 weeks window)

- Weigh the patient before and after delivery
- Collect the delivery data listed in the relevant eCRF
- Collect the neonatal outcome data listed in the relevant eCRF
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Visit 6 – 6 weeks after delivery (± 2 weeks window)

- Ask patient to complete the HFS and DTSQs questionnaires
- Weigh the patient
- Measure the patient's blood pressure

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- Collect the patient's medical data listed in the relevant eCRF
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)
- Terminate pump therapy

Miscarriage – any time

- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Discuss with patient if she wants to continue the same therapy (CSII or SAP)
- Check infusion site, make sure patient uses infusion sets properly (if applicable)
- Make therapy adjustment, and change pump settings, if necessary
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Early dropout – any time

- Ask patient to complete the HFS and DTSQs questionnaires, if patient agrees
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Discuss with patient if she wants to continue the same therapy (CSII or SAP)
- Check infusion site, make sure patient uses infusion sets properly (if applicable)
- Make therapy adjustment, and change pump settings, if necessary
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Inclusion Criteria:

A subject is eligible for the study if the following criteria are met:

1. Female diagnosed with Diabetes Mellitus Type 1
2. Subject indicated by HCP to start insulin pump therapy (CSII) or sensor augmented pump therapy (SAP) due to the desired or established pregnancy
3. HCP has prescribed the use of Orchestra donated device to the subject independently of the study
4. Signed Patient Informed Consent (PIC)
5. Subject is 18 to 45 years old, planning immediate pregnancy (within the next 12 months) or being pregnant within the first trimester until the 16th week of amenorrhea
6. Subject has been on MDI for at least 3 months before starting pump therapy

Exclusion Criteria:

A subject is excluded from the study if any of the following criteria are met:

1. Subject was enrolled in the registry earlier, and terminated it (for any reason)

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2. Participation in any other interventional clinical trial – currently and/or in the last 3 months before the signature of PIC
3. Subject uses an insulin pump that was not donated by the Orchestra Foundation
4. Pregnant women with longer than 16 weeks of pregnancy/amenorrhea
5. Subjects who need assisted in vitro fertilization
6. Subjects with Diabetes Mellitus Type 2, Gestational Diabetes, MODY or any other type of diabetes than Type 1
7. Subject under the age of 18
8. Subject legally incompetent
9. Subject cannot read or write

Study Endpoints:

Data will be collected during routine follow-up visits from pre-conception time, during pregnancy and delivery, up to 6 weeks after delivery and at miscarriage, if any. Some endpoints as described below will be collected from patient medical files retrospectively up to 12 months prior to study start.

Maternal outcomes

- HbA1c (local laboratory) – last value before insulin pump therapy started (retrospective value from patient's medical file), 2-3 values during pregnancy, and one value at the end of the study.
- Proportion of women achieving HbA1c <6.0%, 6.5%, 7%, 7.5% and 8% at each trimester
- Serious adverse events
    - Severe hypoglycaemia (according to the standard definition requiring third party assistance – see point F 5. 1) from the period of 12 months prior to study start until study end
    - DKA from the period of 12 months prior to study start until study end
    - Miscarriage, hospitalization because of uterine bleeding, hospitalization because of instable glycaemia and others
    - Any hospital admission
- Weight, BMI
- Daily insulin use
- Medical information: Microalbumin excretion with albumin/creatinin ratio, blood pressure, parity, folic acid and any other supplementation, White classification, diabetes duration, previous insulin regimen
- Number of SMBG/day (patient self-reported)

- Patient questionnaires:
    - Hypoglycaemia Fear Survey (HFS) collected at enrollment, 2-3 x during pregnancy, and 6 weeks after delivery
    - Diabetes Treatment Satisfaction Questionnaire (DTSQs, status version), collected at enrollment, 2-3 x during pregnancy, and 6 weeks after delivery, and Diabetes Treatment Satisfaction Questionnaire (DTSQc, change version), collected at 24 weeks into pregnancy

- Device Data:
    - Descriptive statistics for SMBG and SG (mean, SD, median, min and max)
    - time spent SG < 50 mg/dL
    - time spent SG between 50-70 mg/dL

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- time spent SG between 70-120 mg/dL
- time spent SG between 120-140 mg/dL
- time spent SG > 140 mg/dL
- time spent SG > 180 mg/dL
- AUC (SG < 70 mg/dl, SG > 180 mg/dl)
- MAGE
- All these parameters daily, 2-hour postprandial and during night (10PM to 7AM)
- Pump Compliance
- Sensor Compliance, if necessary.

Delivery information

- Sensor and pump wear during delivery (yes/no)
- Patient satisfaction with treatment during delivery

Neonatal outcomes

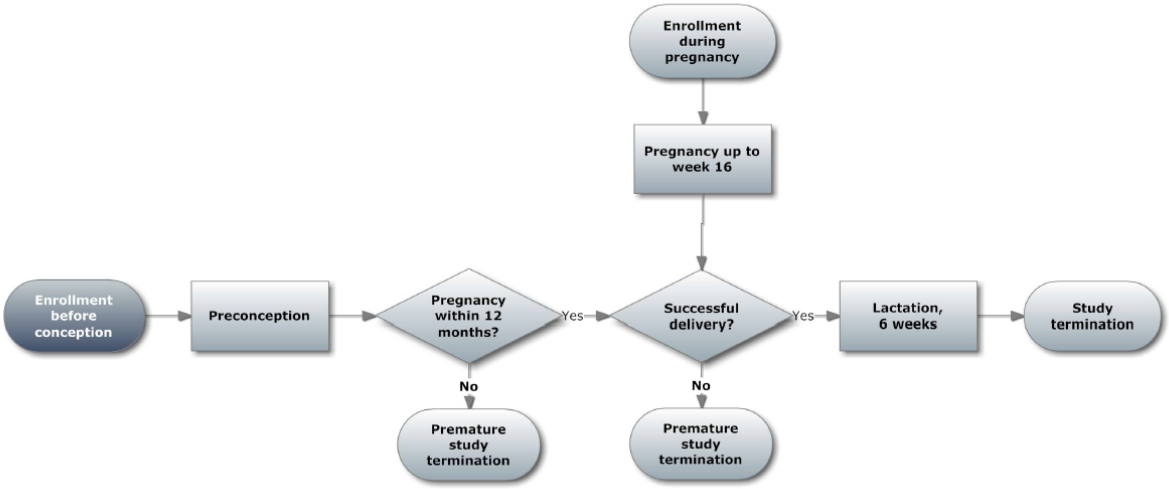
- Mode of delivery (rates elective and emergency Caesarean Section, normal)
- Respiratory distress (1 and 5 minute Apgar scores)
- Gestational age at delivery, % preterm delivery < 37 weeks
- Infant birth weight (SD scores and customised birth weight percentile, % large for gestational age (LGA), % small for gestational age (SGA)
- Neonatal morbidity (treatment for neonatal hypoglycaemia)
- Neonatal care admission (duration of stay, level of care)
- Pregnancy related Serious Adverse Events (miscarriage < 22 weeks, congenital malformation, stillbirth, neonatal death)
- Feeding at hospital discharge (breast, bottle, both)

Timing of data collection into eCRF:

- Baseline
- End of conception trial or after 12 months
- Pregnancy start
- 3 months of pregnancy (12 weeks of amenorrhea ± 4 weeks)
- 6 months of pregnancy (24 weeks of amenorrhea ± 2 weeks)
- 9 Months of pregnancy (36 weeks of amenorrhea ± 2 weeks)
- Delivery (+ 2 weeks)
- 6 weeks after delivery (± 2 weeks)
- Miscarriage any time

Clinical Procedures:

Figure 1: Flow chart of the Enrollment and Termination possibilities depending on the pregnancy



6. Determination of Sample Size

The minimum number of subjects to be enrolled is 100 women with complete follow-up of pregnancy from pre-conception until 6 weeks after delivery. Based on local data and experience, complete follow-up from the pre-conception phase will be possible for about 1/3 of the pregnancies. In about 2/3 of the cases, CSII will start during the first trimester of pregnancy, at the latest on the 16th week.
The expected total sample size is therefore 500 subjects including

- 100 subjects with complete follow-up – all phases on CSII, includingSAP (pre-conception, pregnancy, 6 weeks after delivery).
- 300 subjects with pregnancy (enrollment up to the 16th week of pregnancy) and 6 weeks after delivery
- 100 subject with early termination (for various reasons like miscarriage, no conception within 12 months, etc.)

Enrollment will stop when data from 100 pregnancies with complete follow-up from pre-conception until 6 weeks after delivery have been collected.

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

Number of subject screened enrolled, withdrawal, complete of each pregnancy phase and study will be reported. The number of subjects assigned to CSII/SAP group, with or without sensor will also be provided as overall and for each center.

7.1.2. Clinical Investigation Plan (CIP) Deviations

All protocol deviations will be presented in the listings.

7.1.3. Analysis Sets

All enrolled subjects who have participated in Orchestra Pregnancy Observational Study in Poland will be included in the efficacy analysis population. All enrolled subjects will be included in the safety analysis population.

7.2. General Methodology

All data from the time of screening until the end of the study will be collected either on eCRFs or electronically by uploading the various devices. Data and analysis will be summarized in a Clinical Study Report.

No statistically powered analyses or hypothesis testing will be performed. Summary and descriptive statistics will be performed.

7.3. Center Pooling

Up to 23 investigational centers will be used during this study. Data will be pooled for analysis

7.4. Handling of Missing Data and Dropouts

No imputation will be used for missing data

7.5. Adjustments for Multiple Comparisons

Not Applicable.

7.6. Demographic and Other Baseline Characteristics

Baseline information and demographic characteristics such as age, gender, weight, BMI, diabetes duration, insulin regimen, etc. will be summarized. Medical information such as previous severe hypoglycemia and DKA history up to 12 month prior to study start will also be summarized.

7.7. Treatment Characteristics

Not Applicable

7.8. Interim Analyses

Not Applicable.

7.9. Evaluation of Objectives

- ***Analysis of Primary Objectives***

Descriptive analysis will be performed for all available groups: 1) all enrolled; 2) those who failed to achieve a pregnancy; 3) those who become pregnant after the pre-conception phase; 4) those who already pregnant and enrolled after.

Glycemic control measured by HbA1c

Calculate descriptive statistics for HbA1c

- A1C and change of A1c
  - from baseline
  - each Pregnancy trimester
- Proportion of subjects achieving A1C < 6% (6.5%, 7%, 7.5%, 8%)

Glycemic Control measured by Continuous Glucose Monitoring Data (for subjects with available sensor data (SG) only)

Calculate descriptive statistics for Sensor glucose distribution , the following variables will be analyzed as overall and stratified by pregnancy outcome (no conception, delivery, miscarriage, etc.) and completeness of treatment phase (complete follow-up, pregnancy and 6 weeks after delivery, pre-conception phase only, etc.)

- Mean SG per subject per day
- SG variation (CV, SD, MAGE) per subject per day
- % of SG < 50mg/dL, 50-60mg/dL, 60-70mg/dL, 70-120mg/dL, 120-140mg/dL, 140-180mg/dL, 180-250mg/dL and > 250mg/dL per subject per day
- AUC of SG < 50mg/dL, < 60mg/dL, < 70mg/dL, > 140mg/dL, >180mg/dL and > 250mg/dL per
- Pregnancy trimester
- Duration of treatment received
- Sensor compliance (% of time sensor wear) in SAP group only

The analysis will be repeated for listed variables based on 2-hour postprandial CGM data and night only (10pm to 7am) data.

Glycemic Control measured by SMBG Data

Calculate descriptive statistics for SMBG distribution , the following variables will be analyzed as overall and stratified by pregnancy outcome (no conception, delivery, miscarriage, etc.) and completeness of treatment phase (complete follow-up, pregnancy and 6 weeks after delivery, pre-conception phase only, etc.)

- N, Mean, Median, SD, Min and Max per subject per day

per

- Pregnancy trimester
- Duration of treatment received

- ***Analysis of Secondary Objectives***

Pregnancy Outcomes

Calculate incidence rates for the following events as overall and by duration of treatment received.

- Mode of Delivery
  - Normal
  - Elective CS
  - Emergency CS
- Preterm Delivery (< 37 weeks)
- Miscarriage (< 22 weeks or >= 22 weeks)
- Neonatal Morbidity
  - Neonatal Hypoglycaemia
  - Other
- Other Pregnancy Related Serious Adverse Events

Neonatal Outcomes

Calculate descriptive statistics for the following as overall and by duration of treatment received.

- Respiratory Distress
  - 1 and 5 minute Apgar scores
- Infant Birth Weight

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- SD scores
- Customised birth weight percentile (LGA, SGA)

Provide frequency tables for the following variables

- Neonatal Morbidity
  - Treatment for Neonatal Hypoglycaemia
- Neonatal Care Admission
  - Duration of Stay
  - Level of Care
- Feeding at Hospital Discharge
  - Breast
  - Bottle
  - Both

Questionnaire and Surveys

The questionnaire and survey results will be presents and by time of questionnaire/survey collected

- Hypoglycaemia Fear Survey (HFS)
- Diabetes Treatment Satisfaction Questionnaire
  - DTSQs
  - DTSQc

Other Maternal Outcomes

Calculate descriptive statistics for the following variables

- Weight
- BMI
- Daily Insulin Requirements (units) at the moment of the visit
- Microalbumin excretion with albumin/creatinine ratio
- Number of SMBG per subject per day (patient self-reported)

per

- Pregnancy trimester
- Duration of treatment received

7.10. Safety Evaluation

All site reported adverse events for enrolled subjects will be summarized, including:

- Incidence of severe (clinical) hypoglycemia
- Incidence of DKA
- Serious adverse events (SAE)
- Unanticipated device effects (UADE)

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Detailed information of all adverse events will be provided in listings. The summary of adverse events will also be provided per trimester.

7.11. Health Outcomes Analyses

Not Applicable

7.12. Changes to Planned Analysis

Not Applicable

8. Validation Requirements

Level I validation is required for Statistical and SAS programming of primary endpoint. Level I requires that the peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer.

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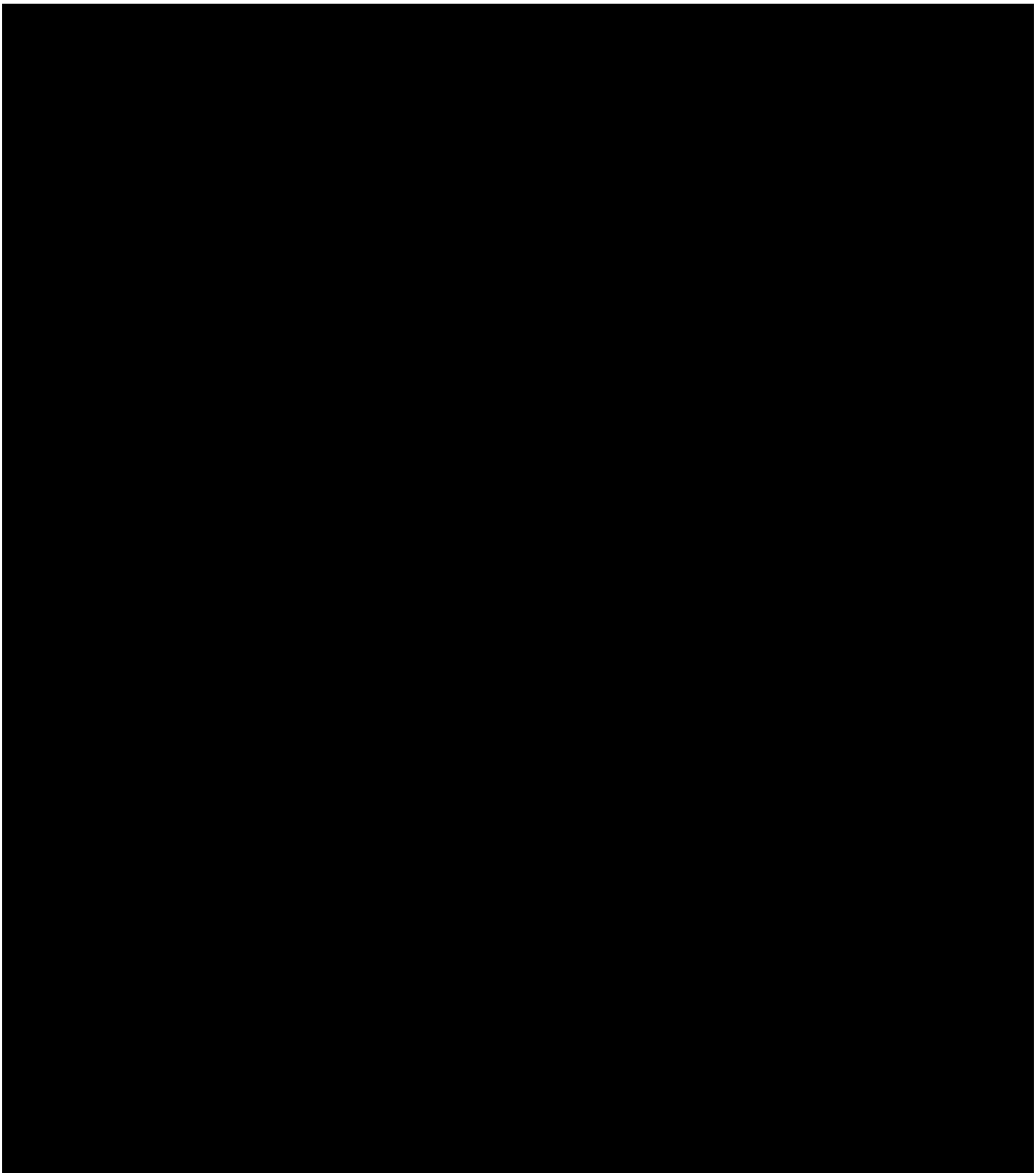

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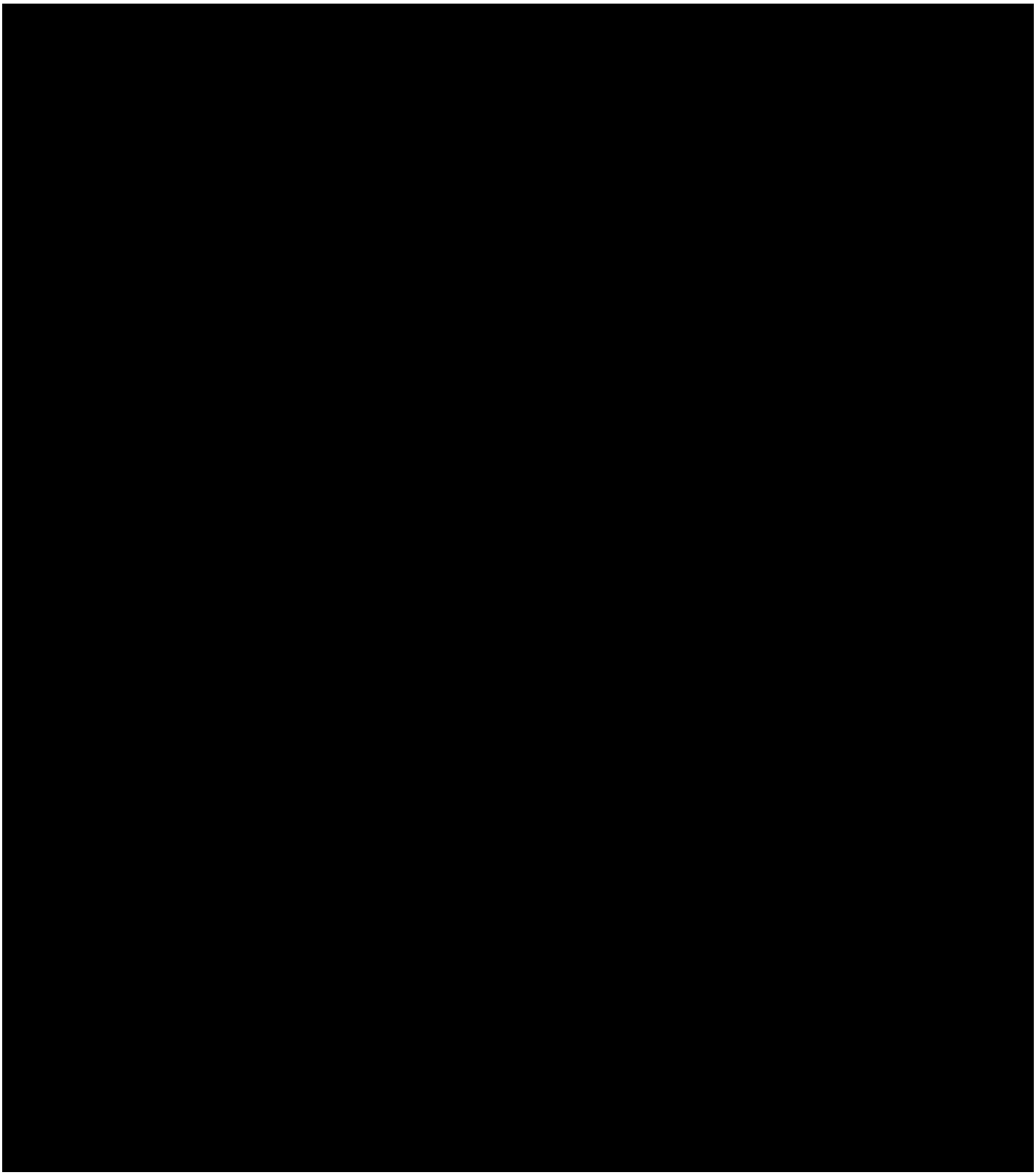

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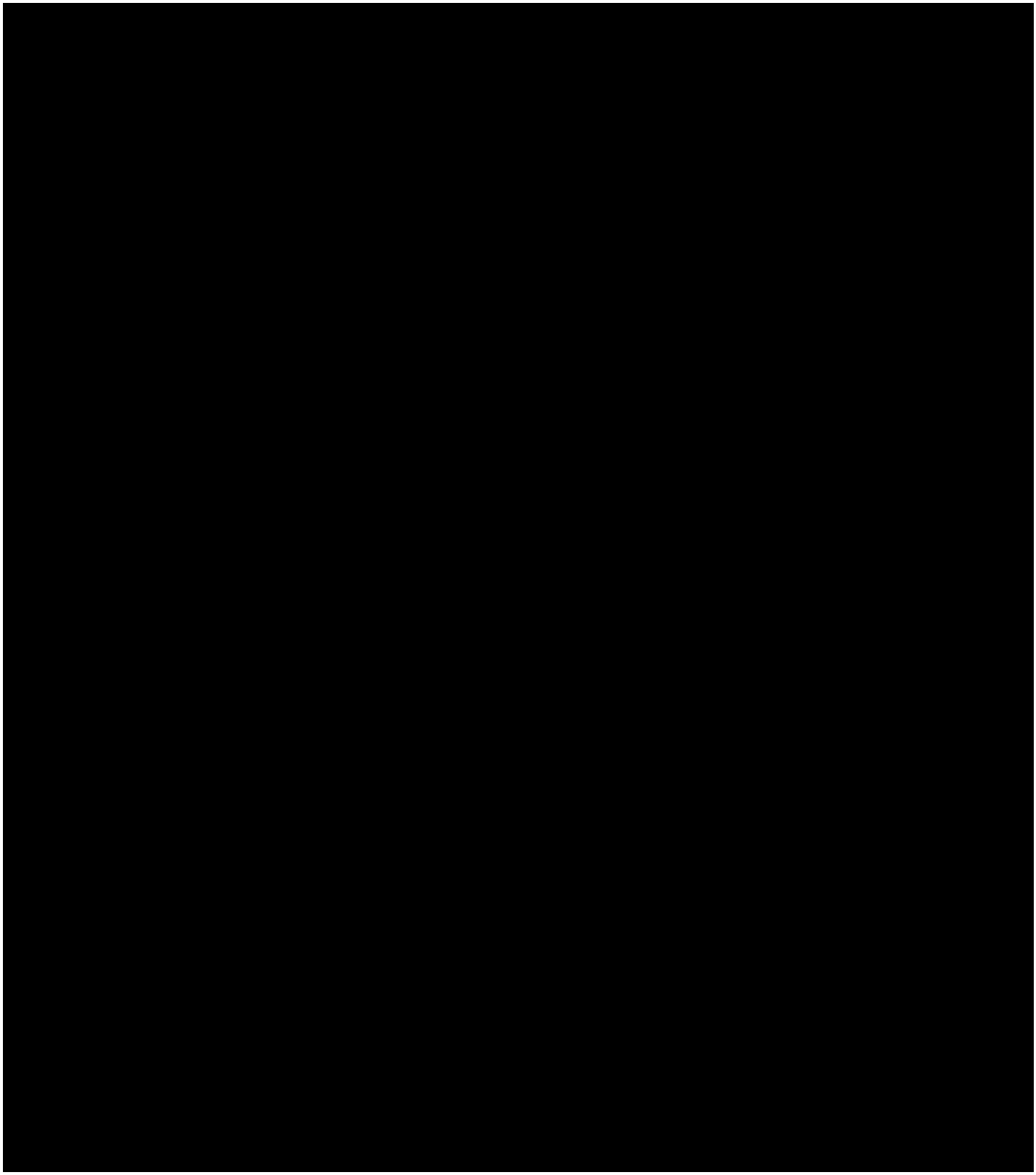

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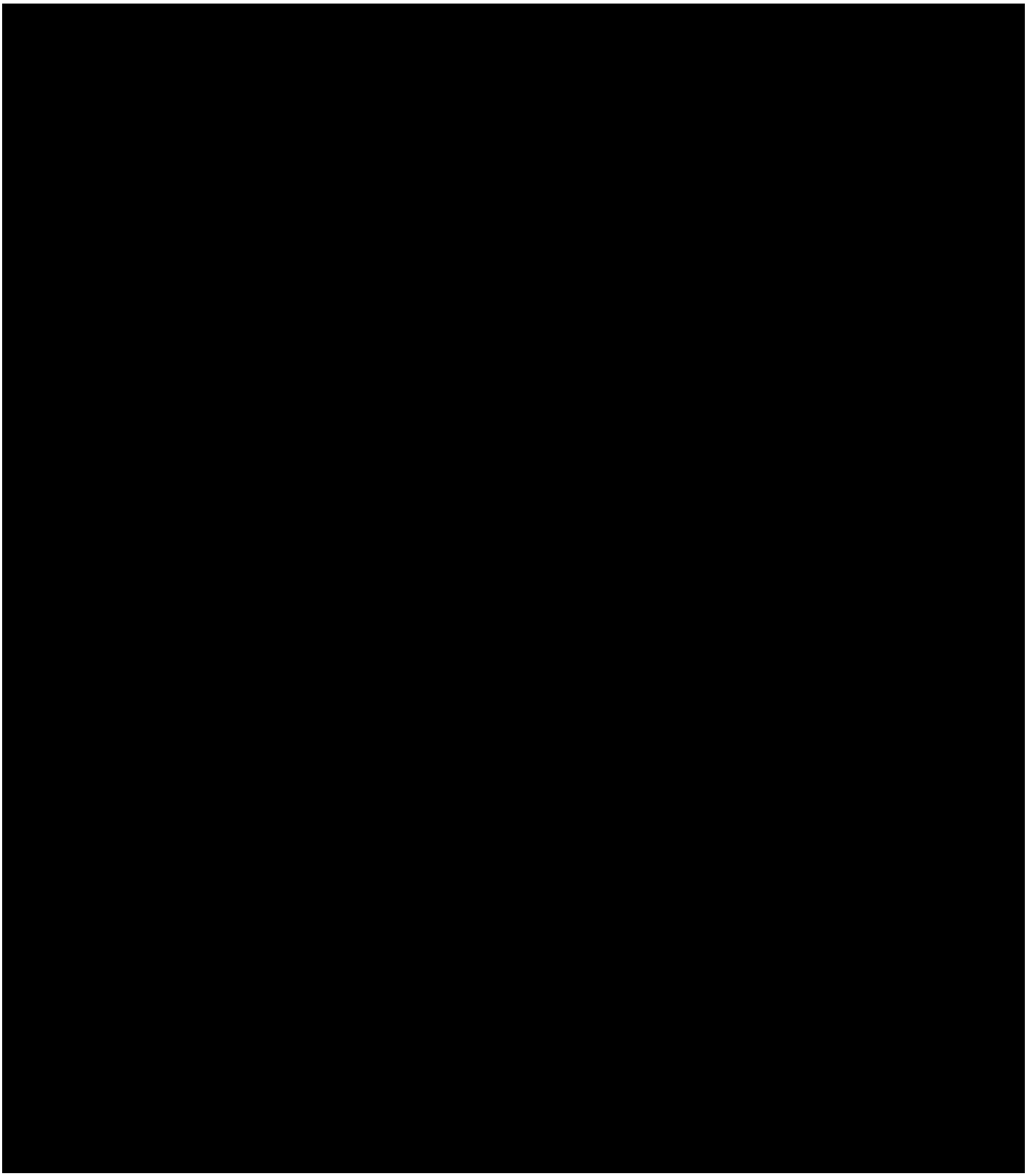

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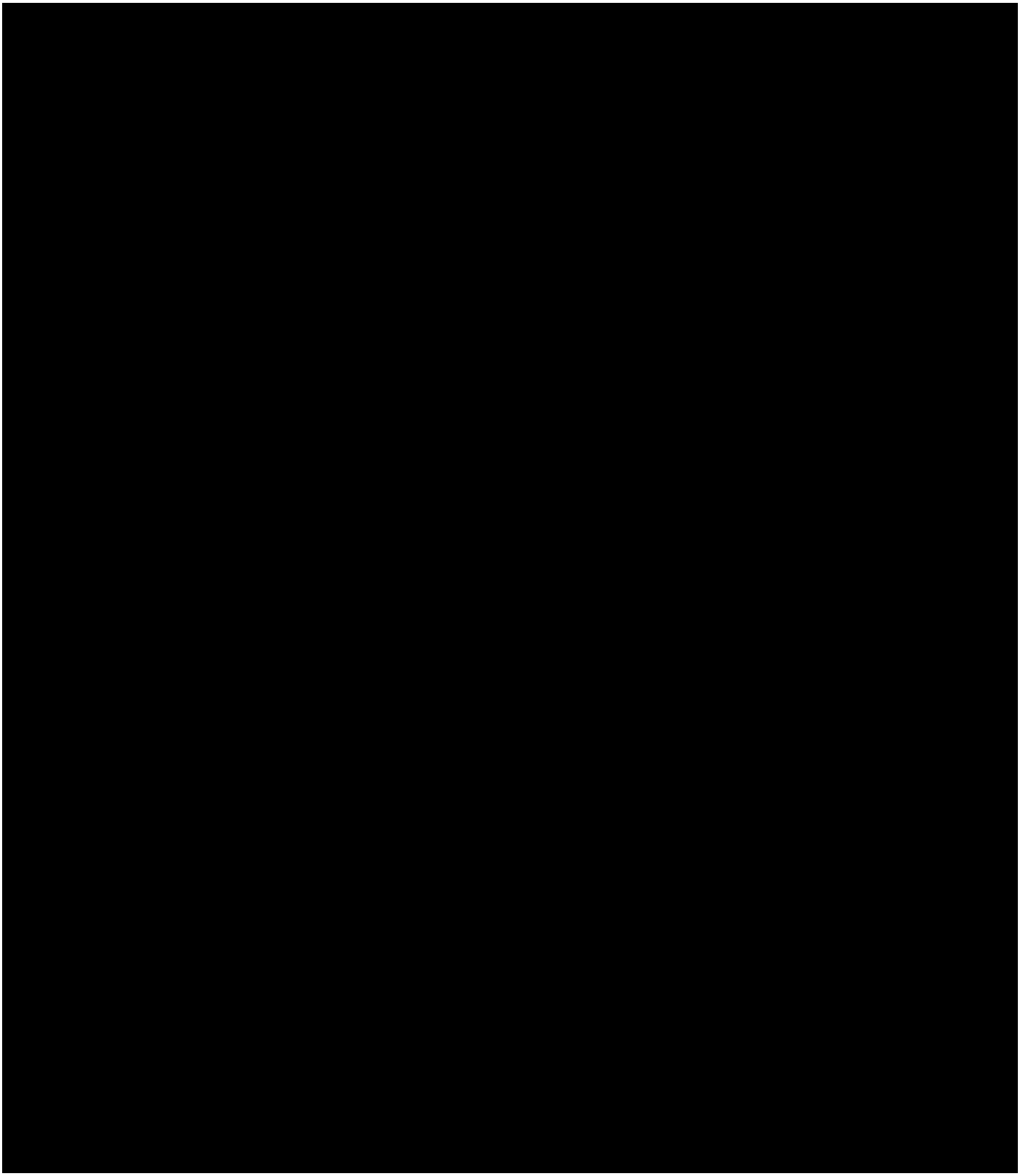

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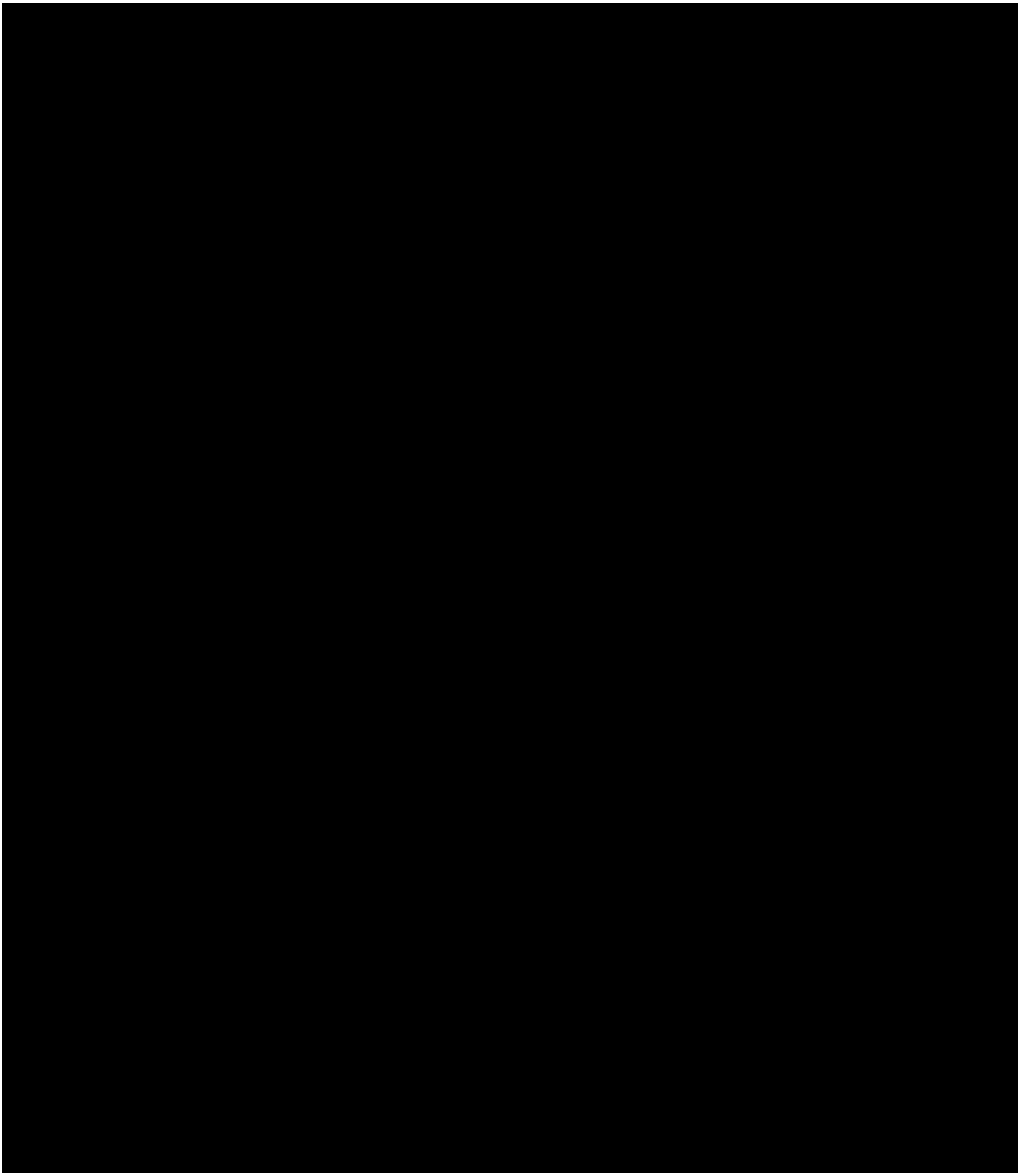

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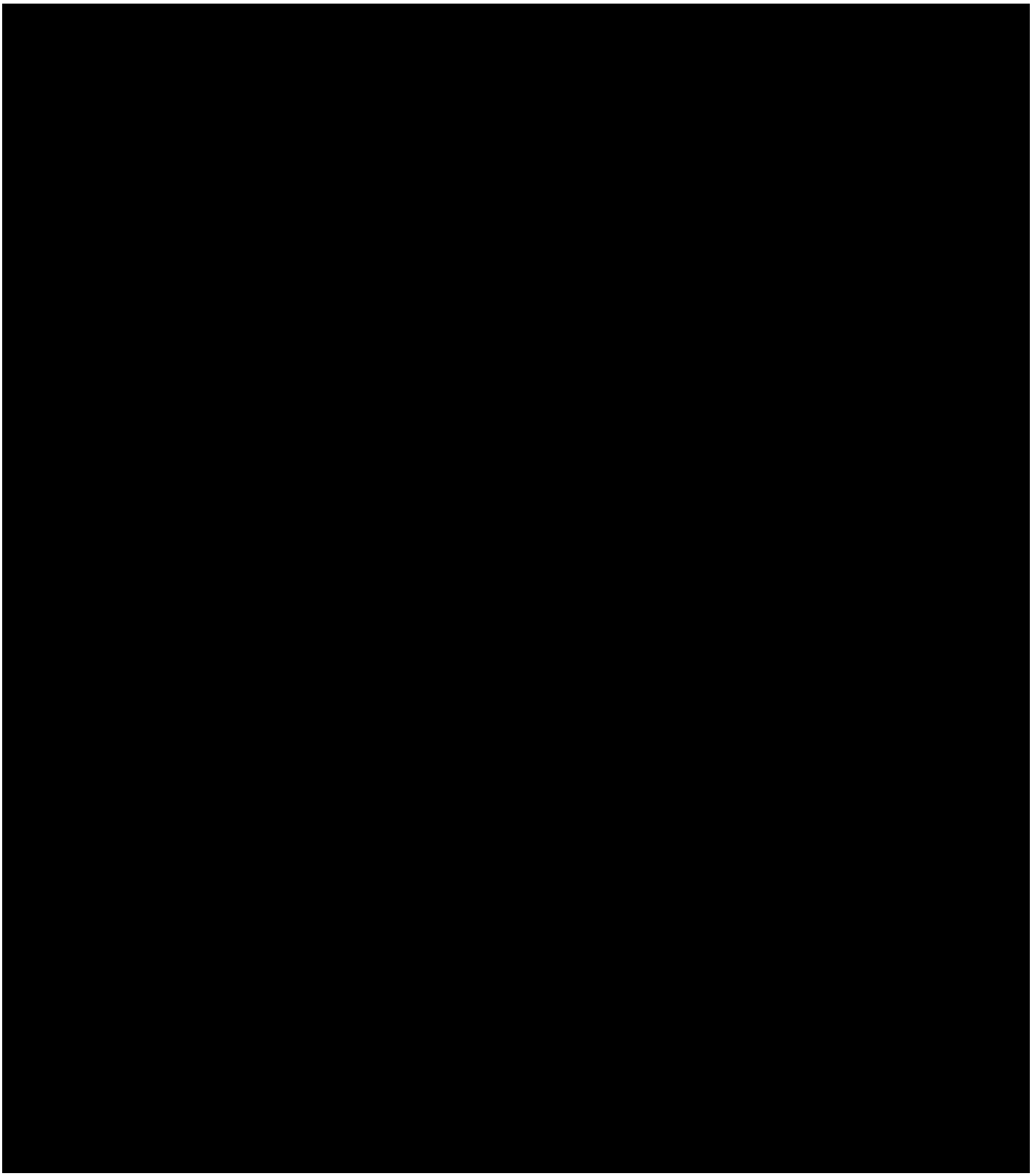

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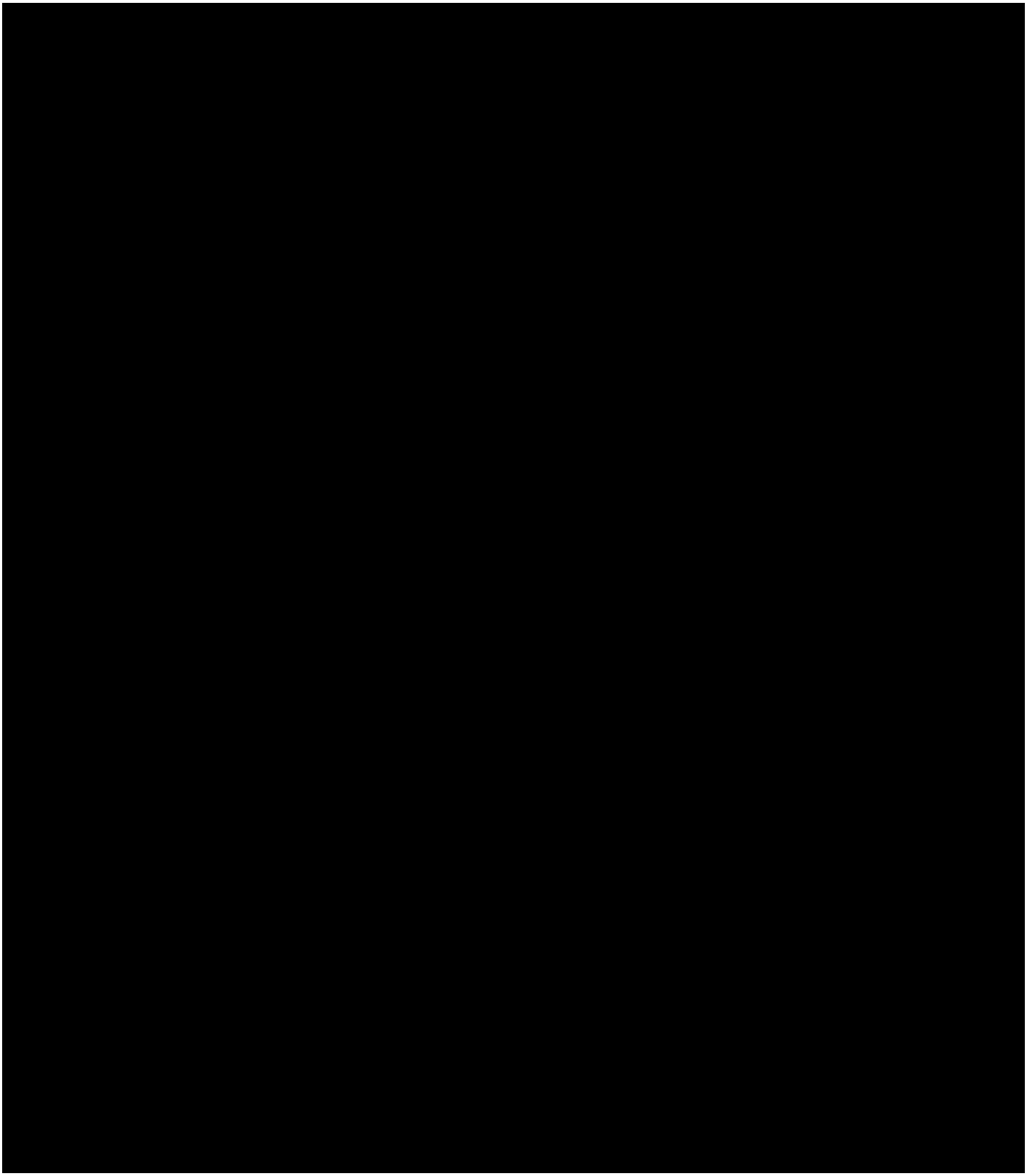

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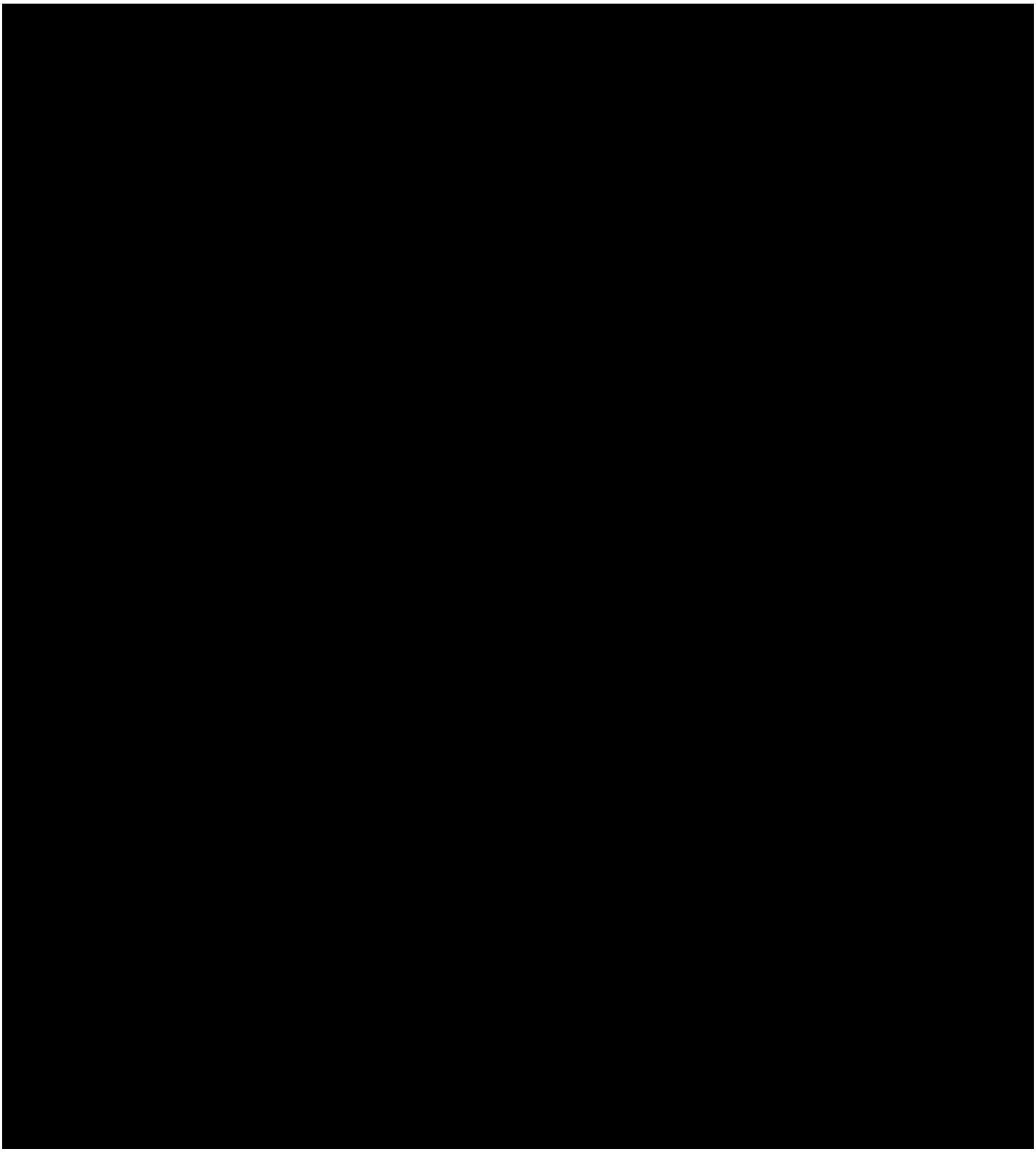

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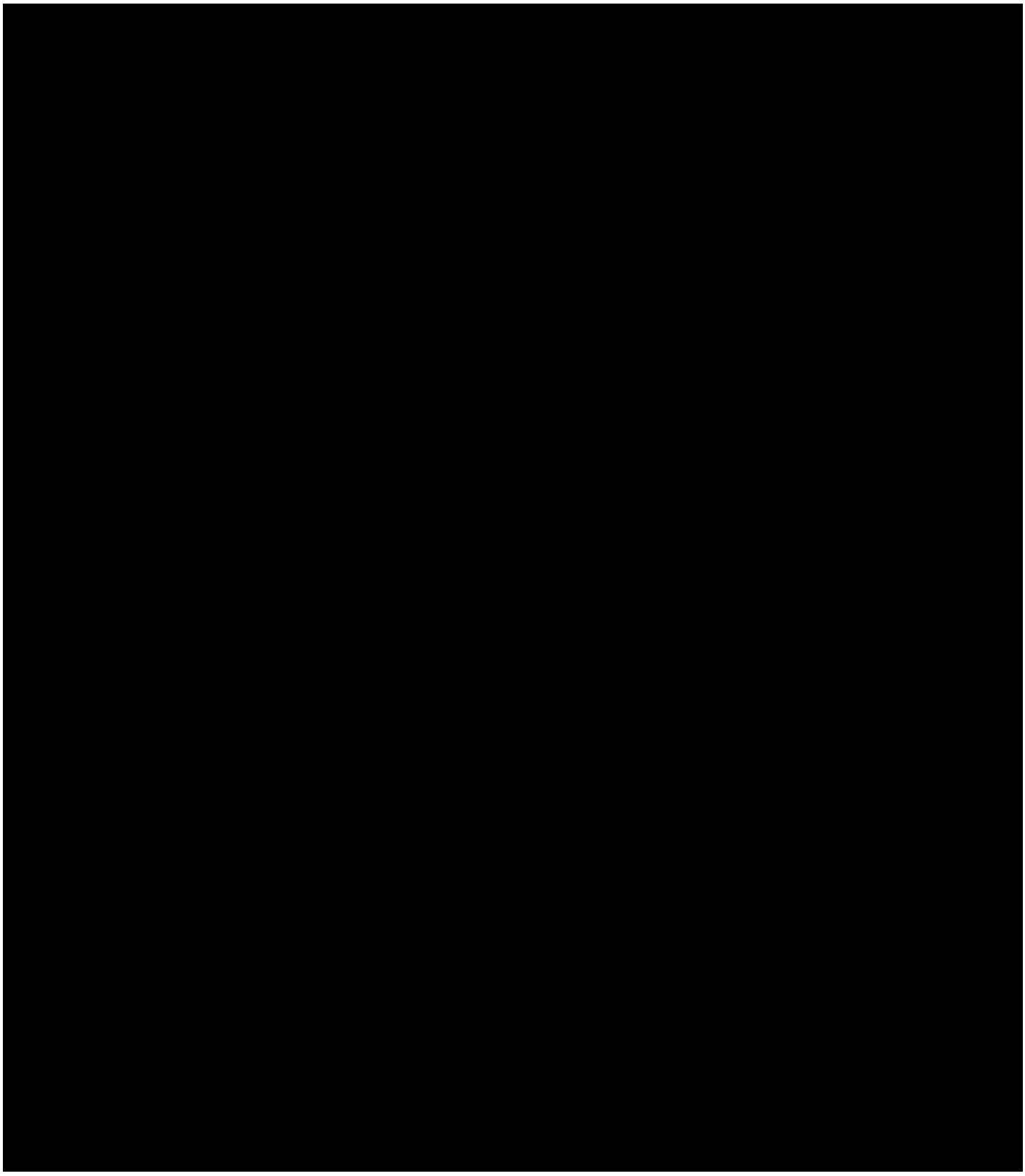

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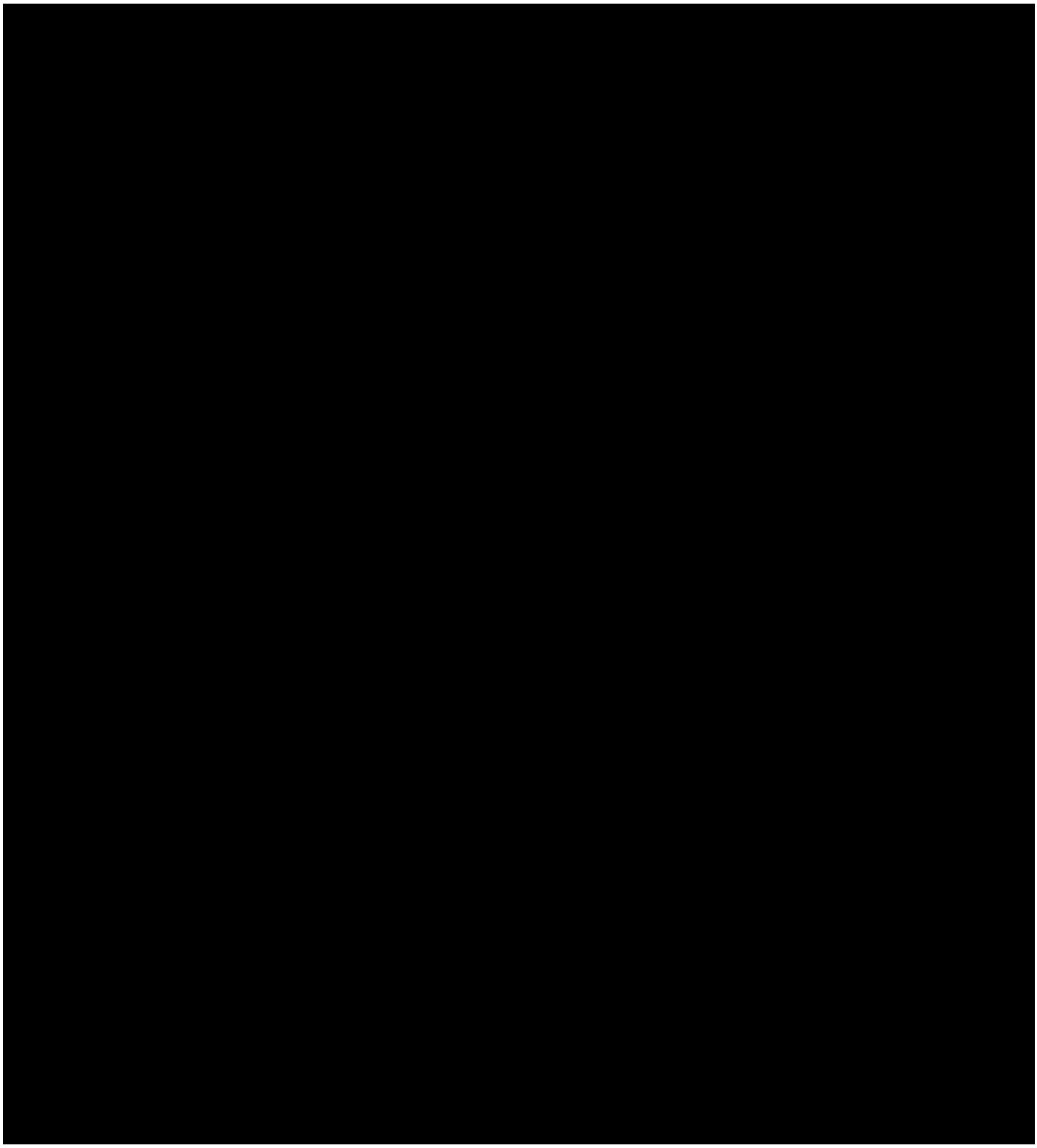

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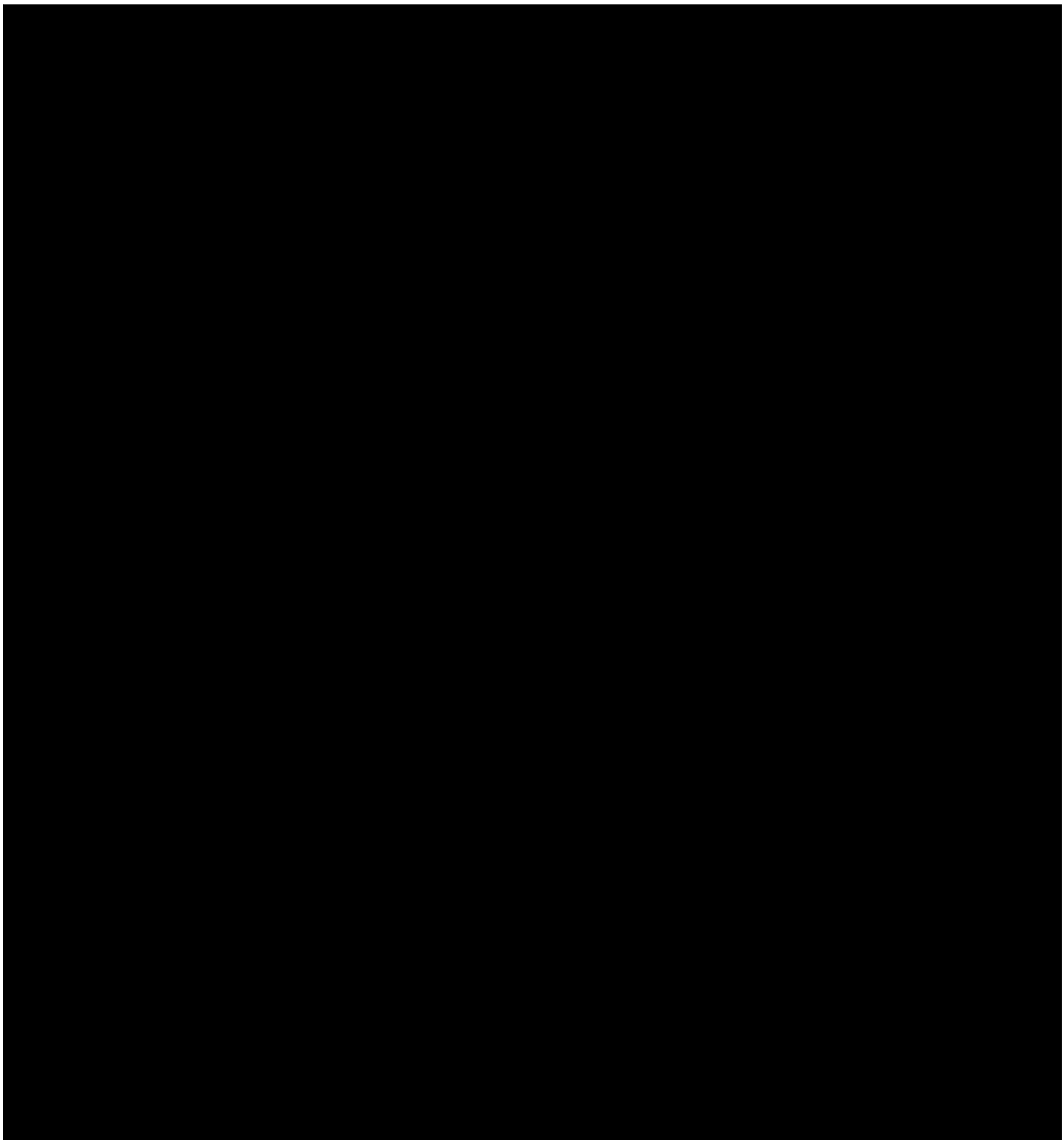

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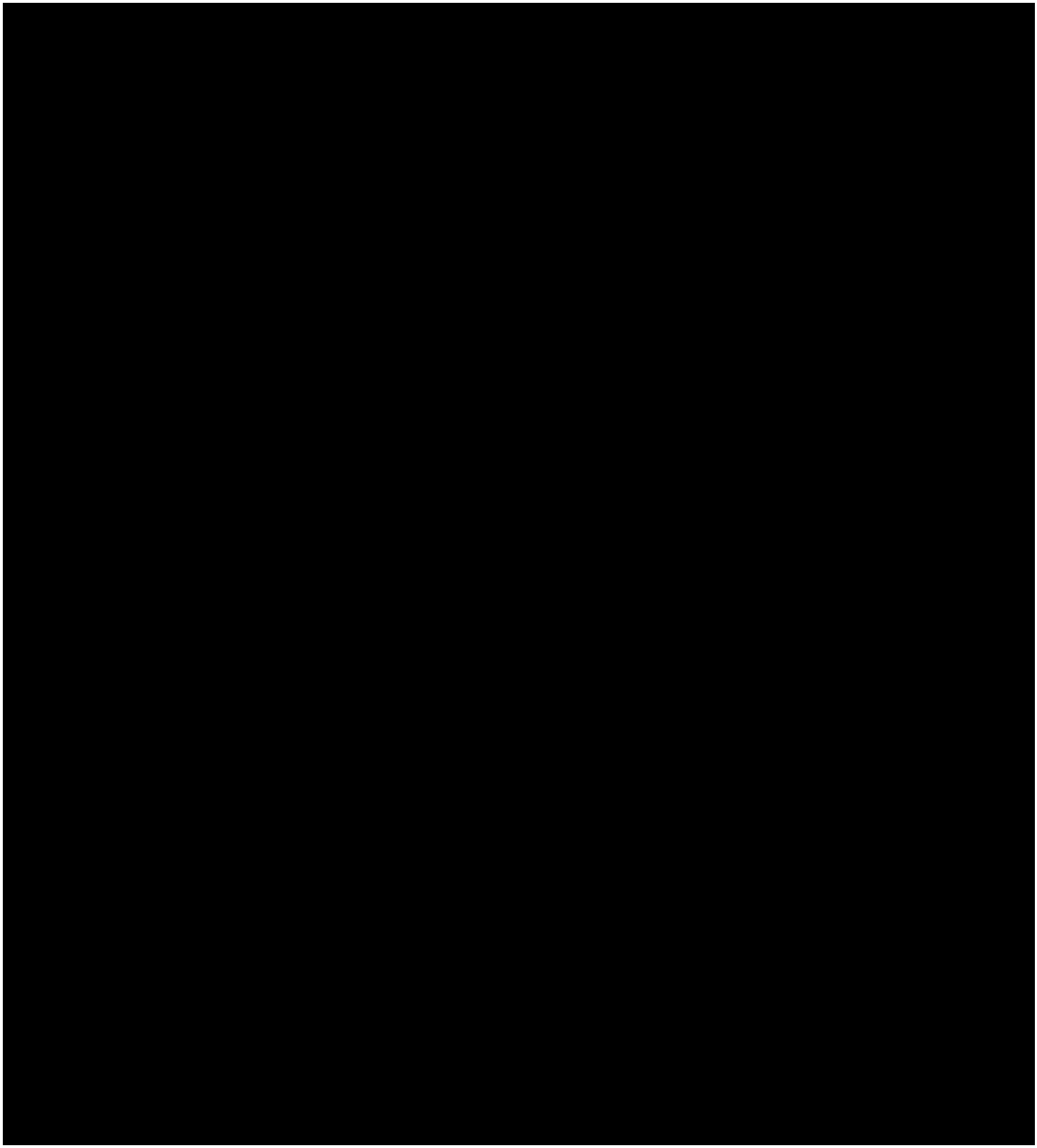

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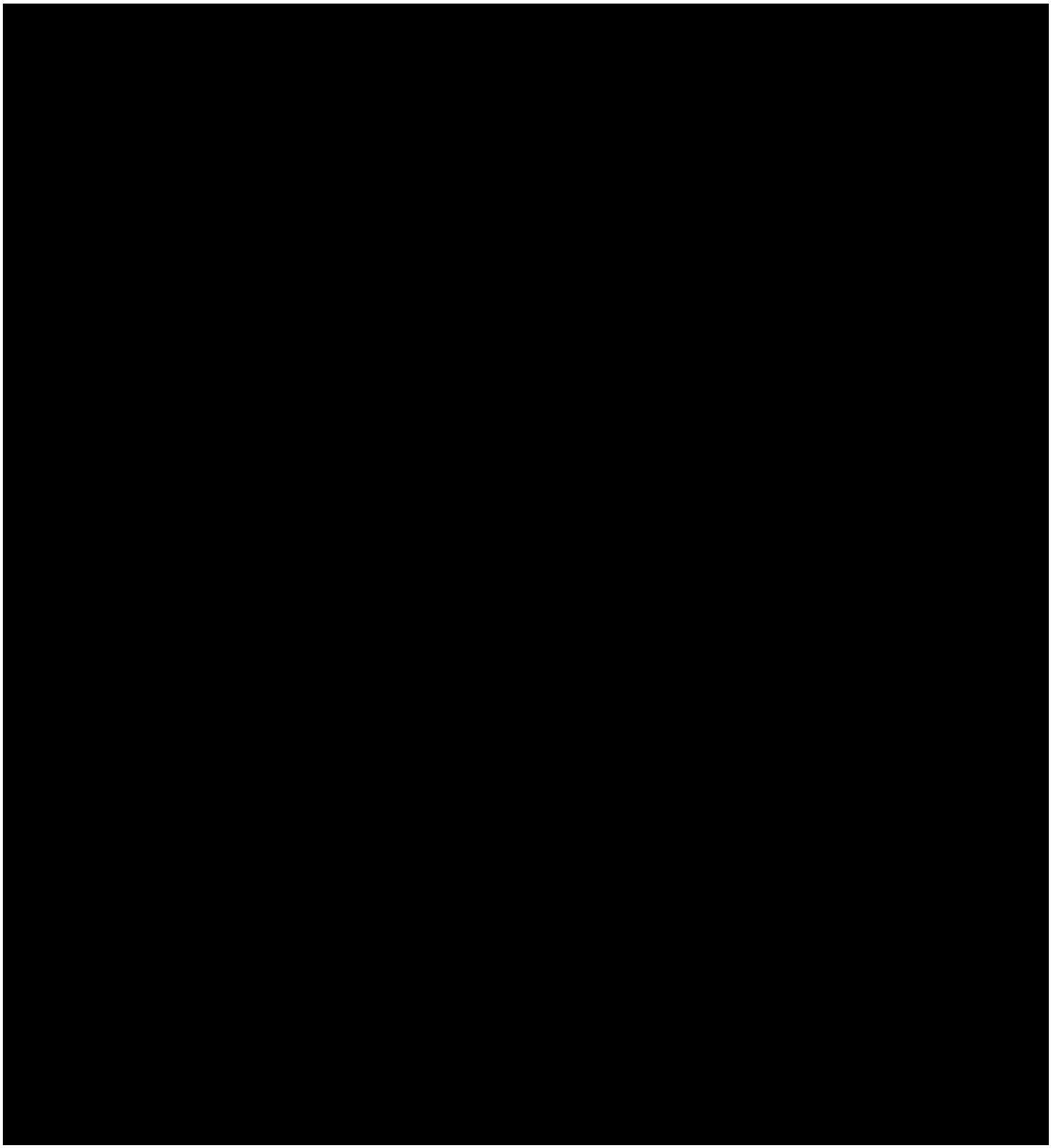

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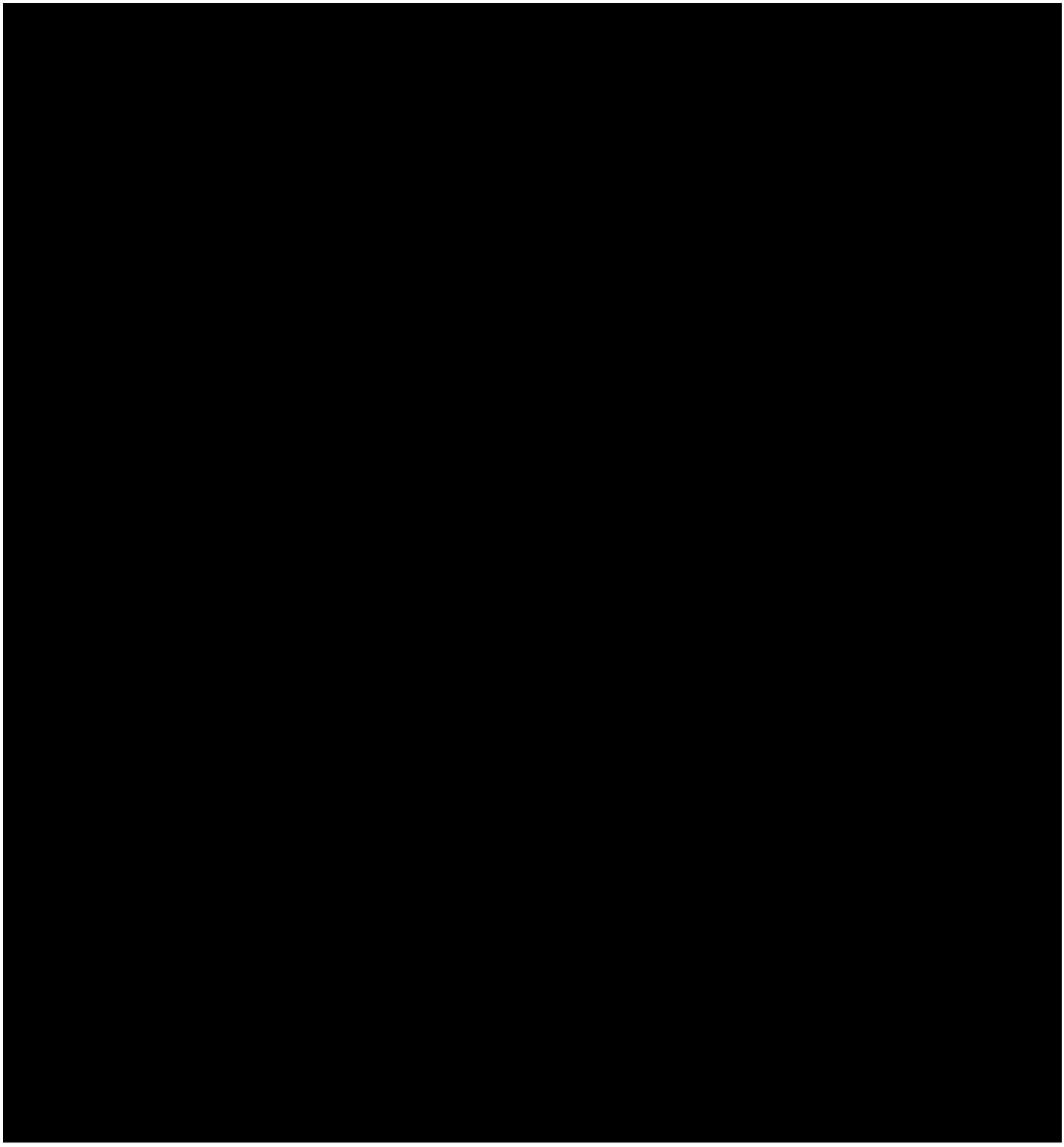

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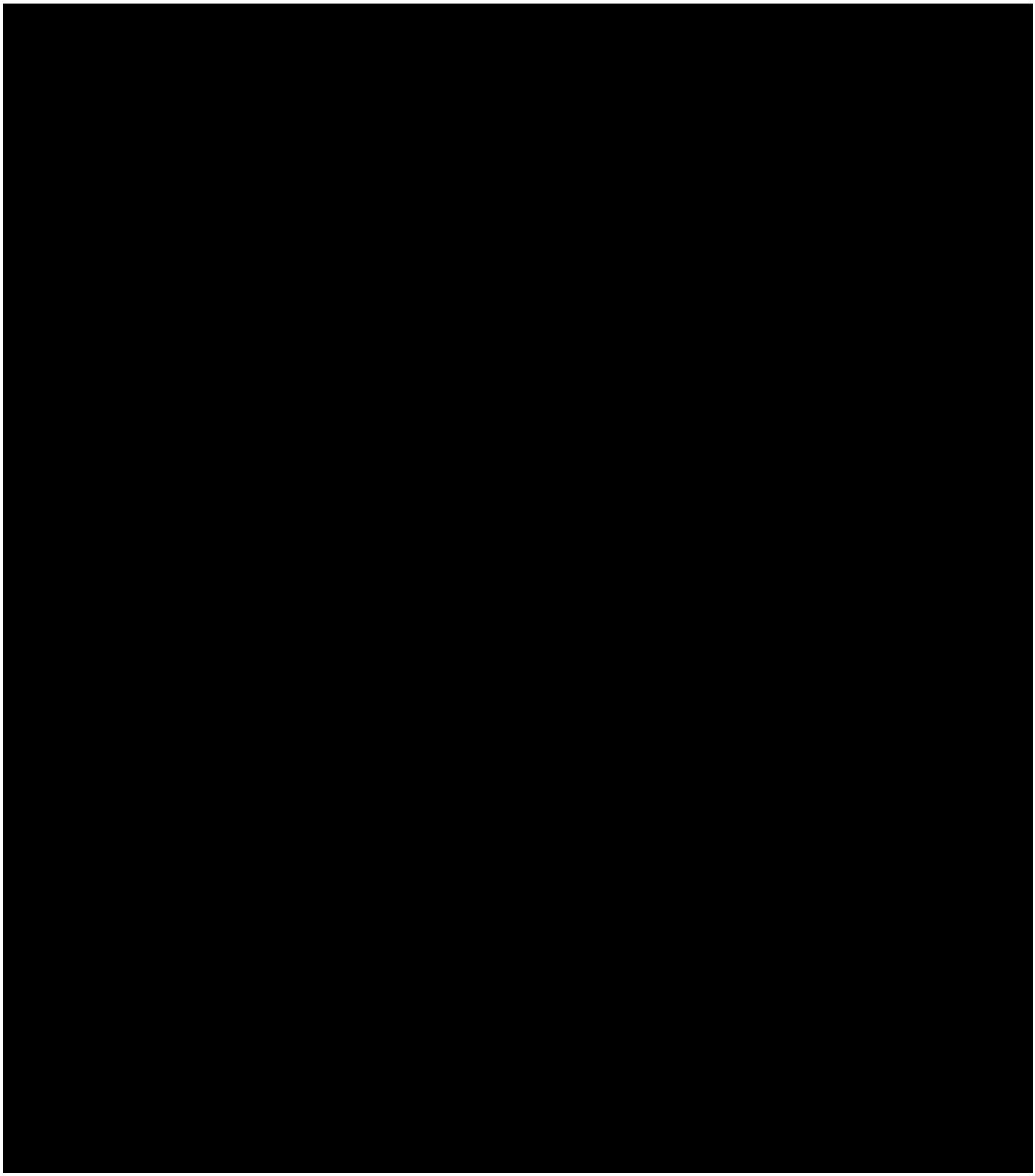

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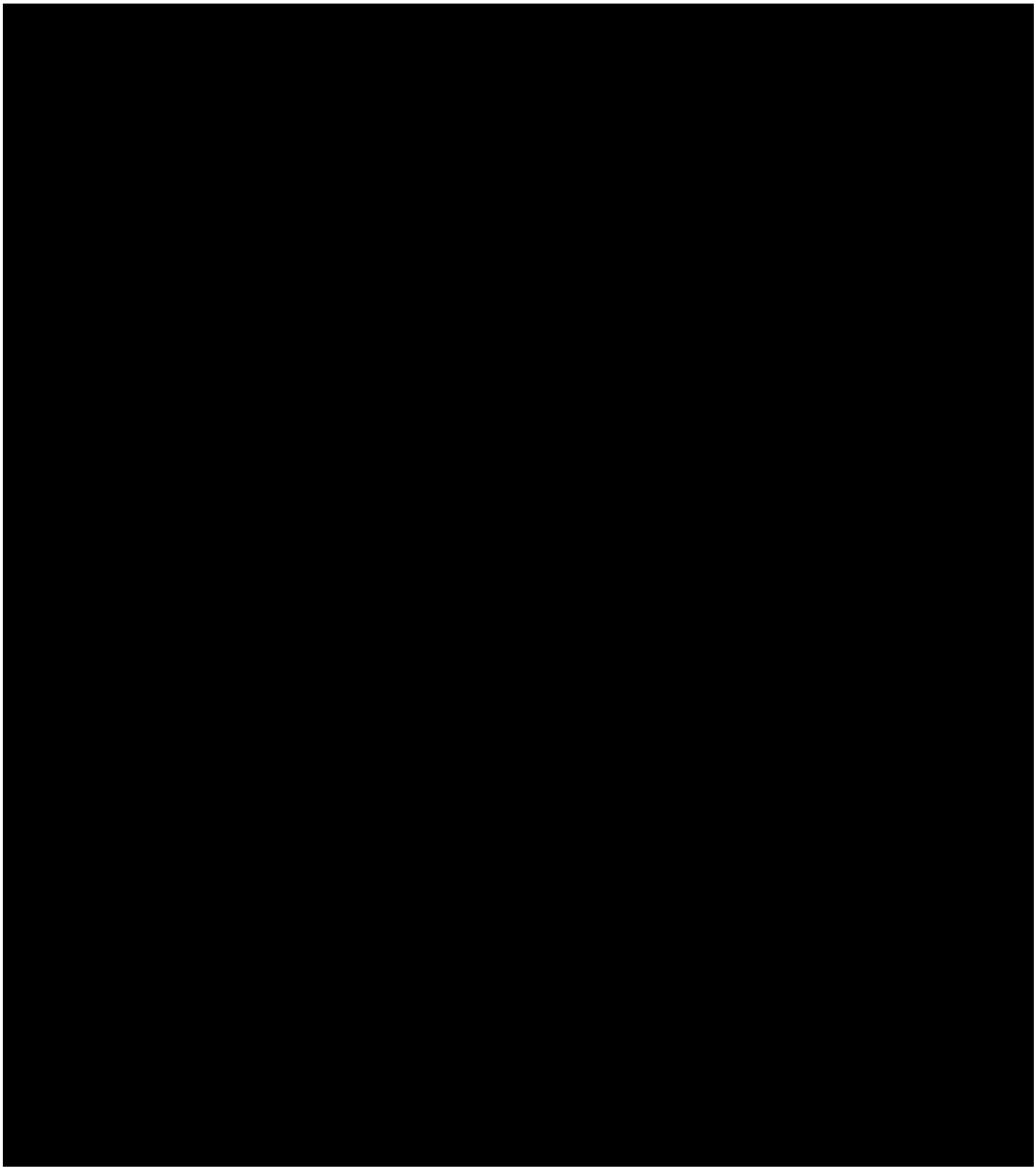

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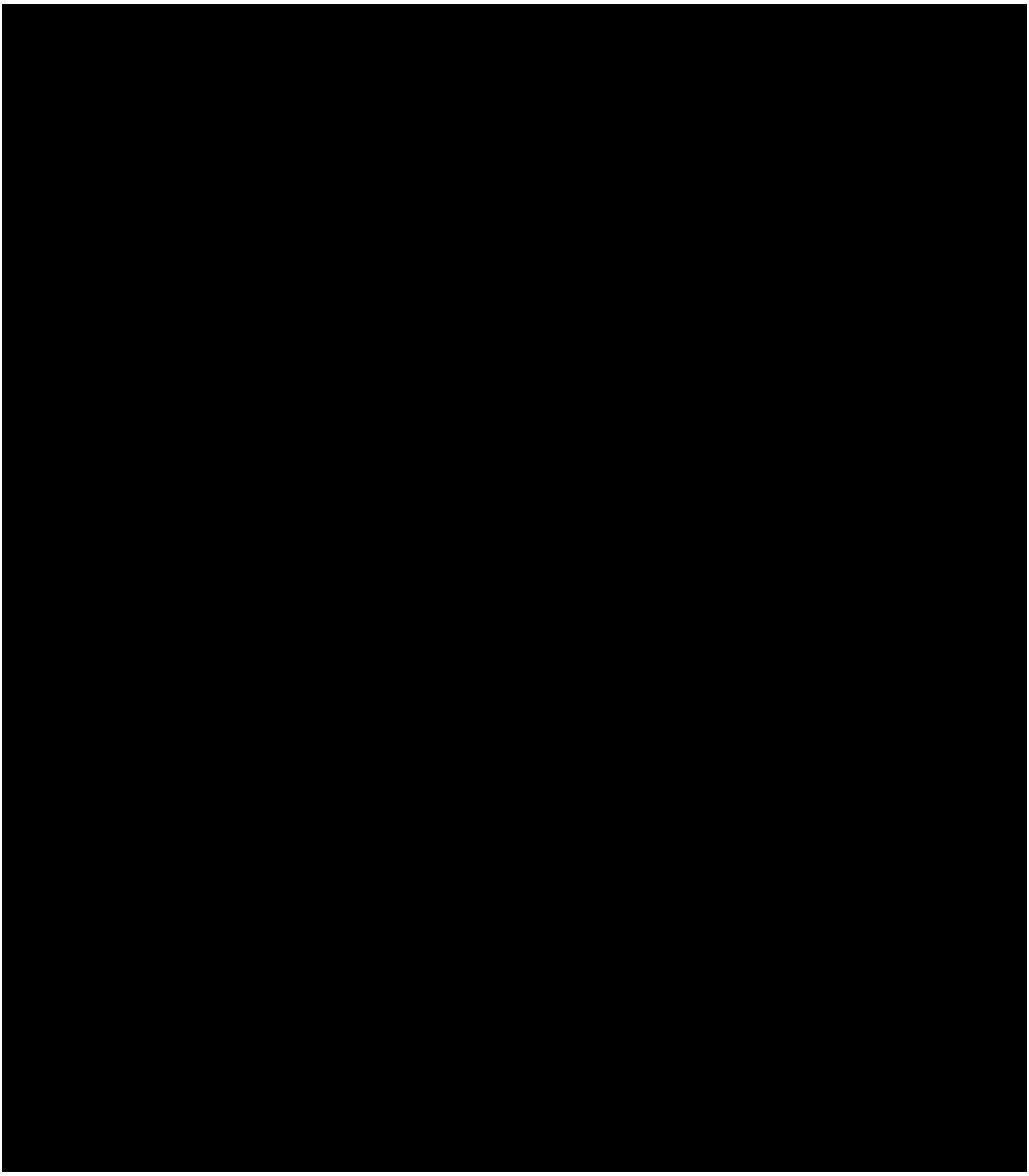

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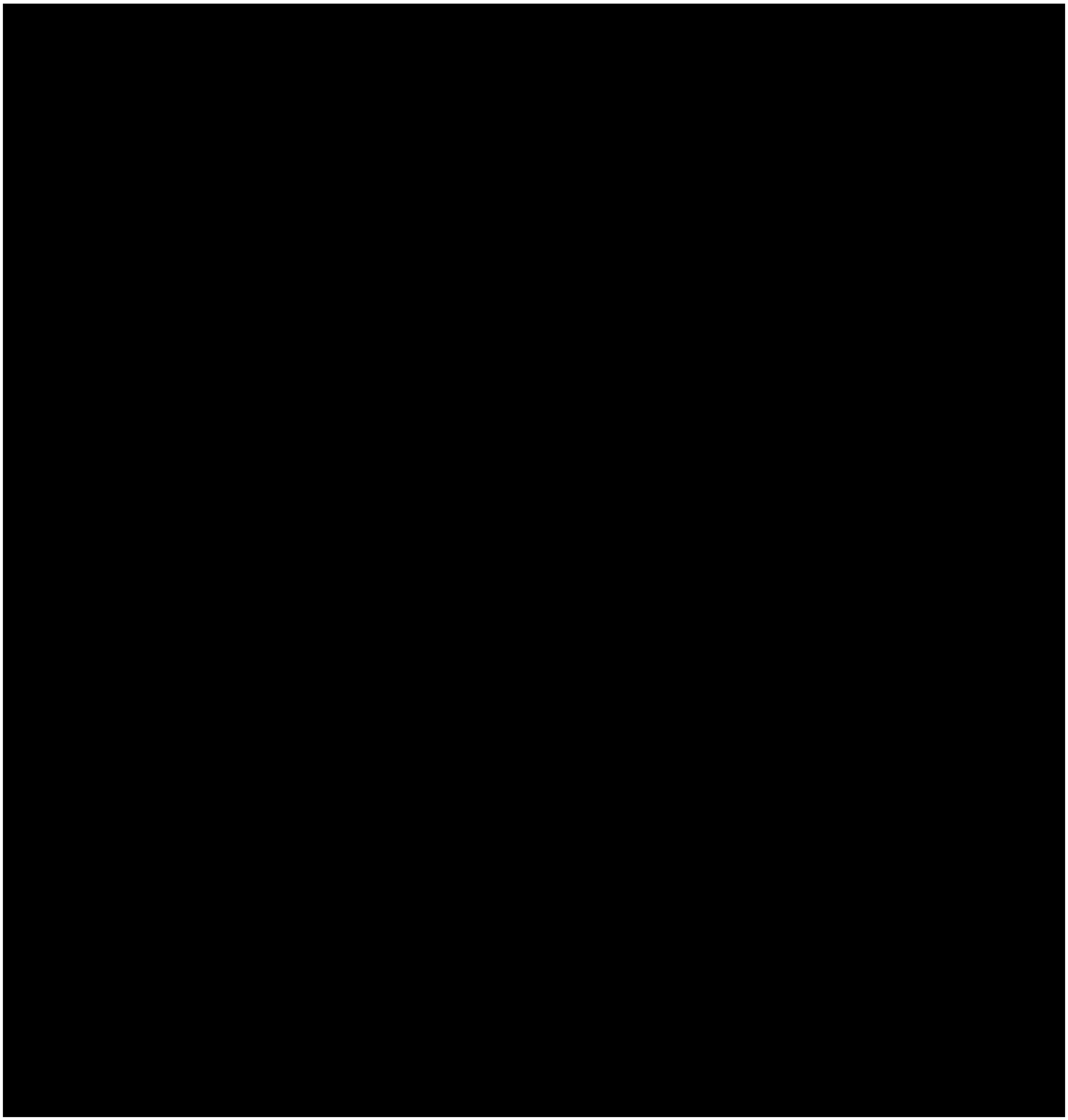
Table X. Neonatal Data after Six Weeks (Overall)



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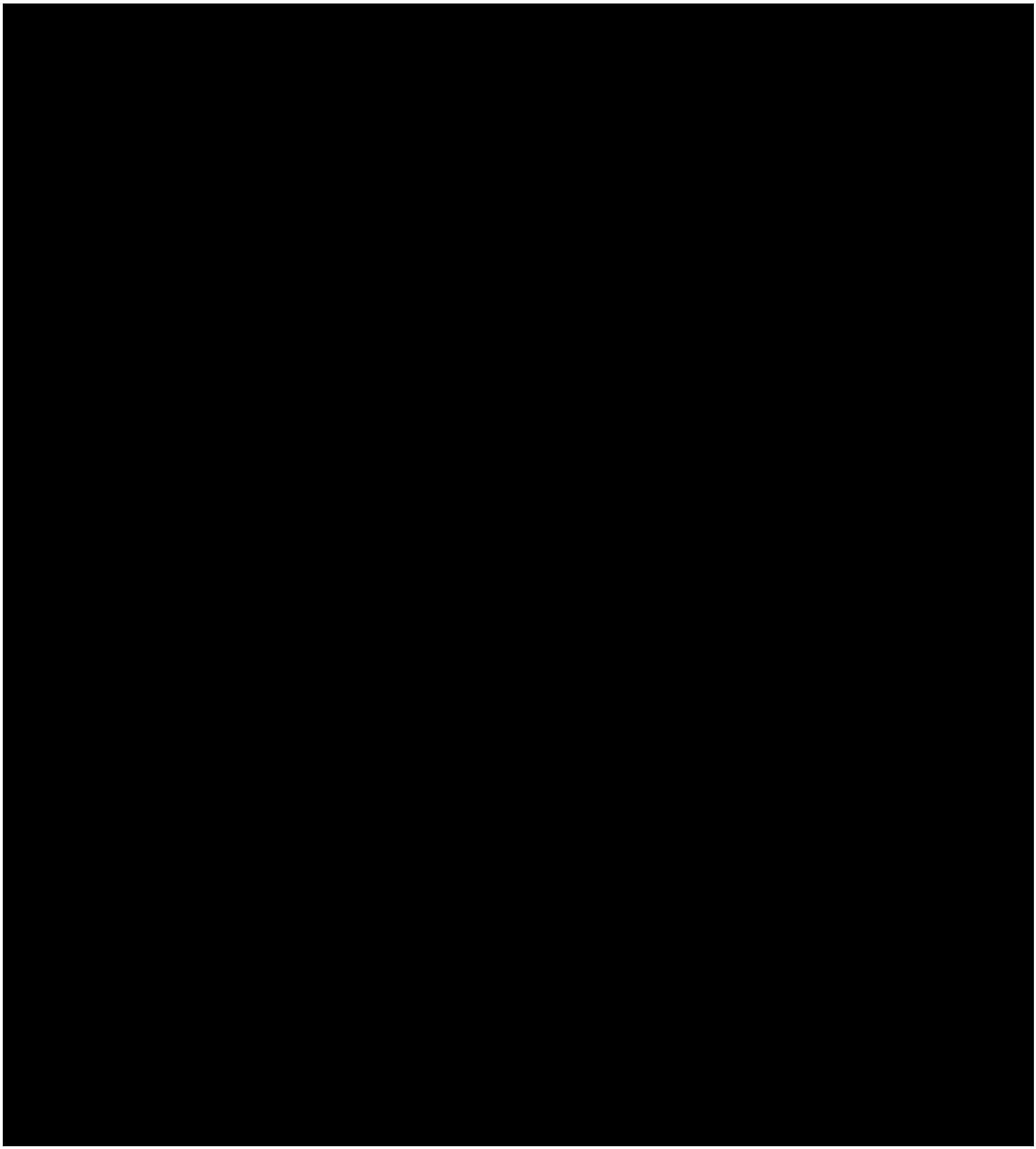

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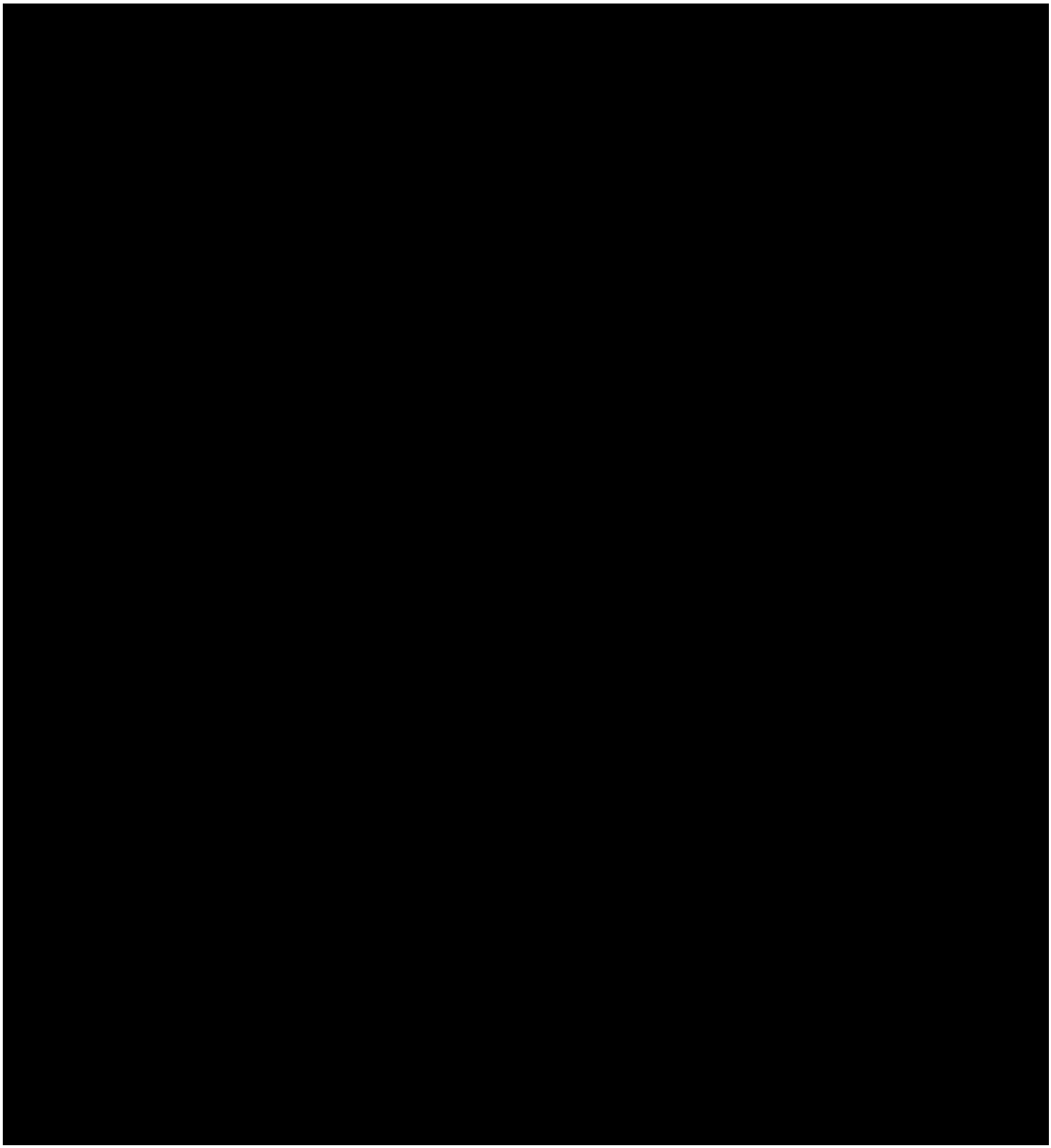

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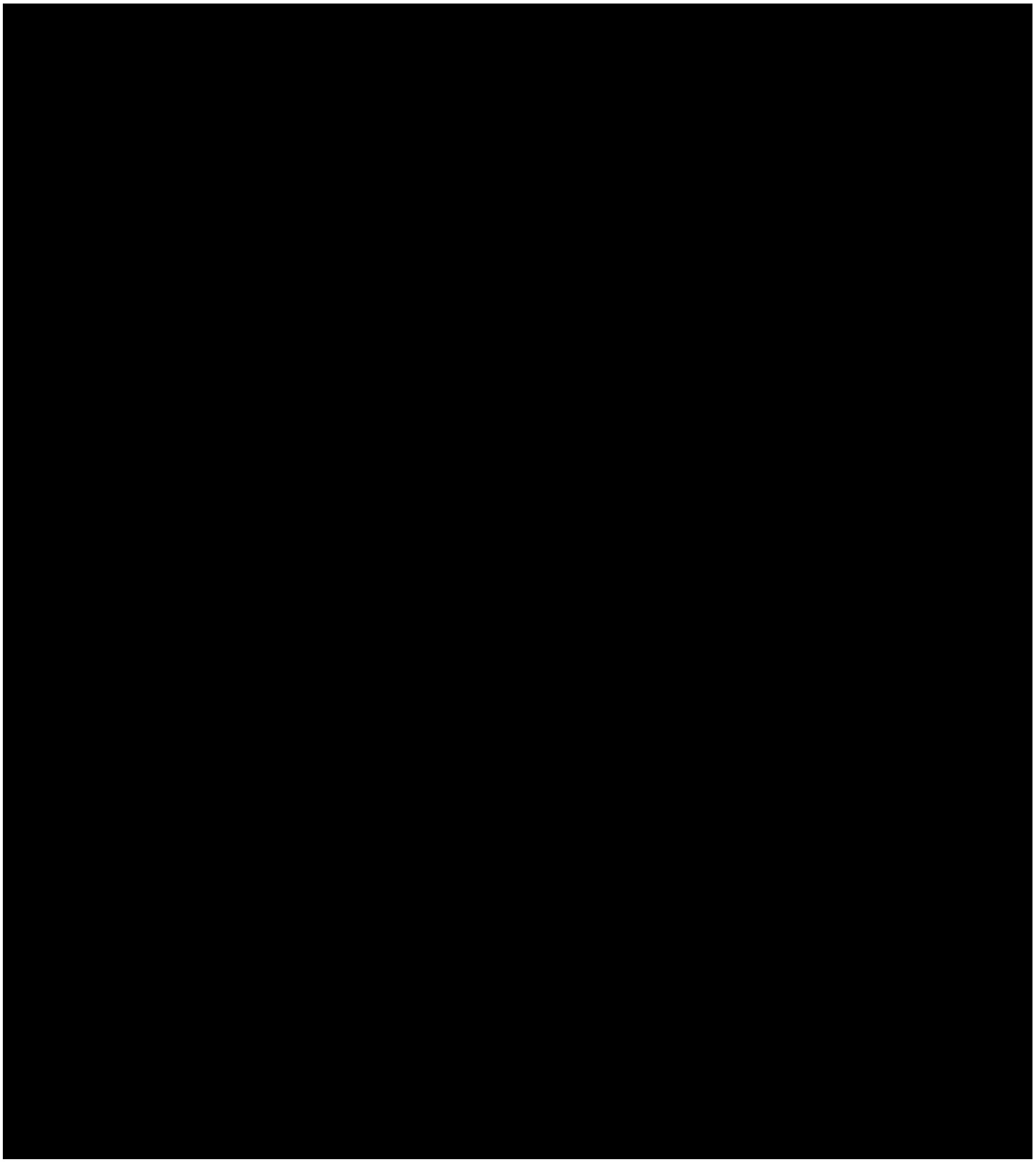

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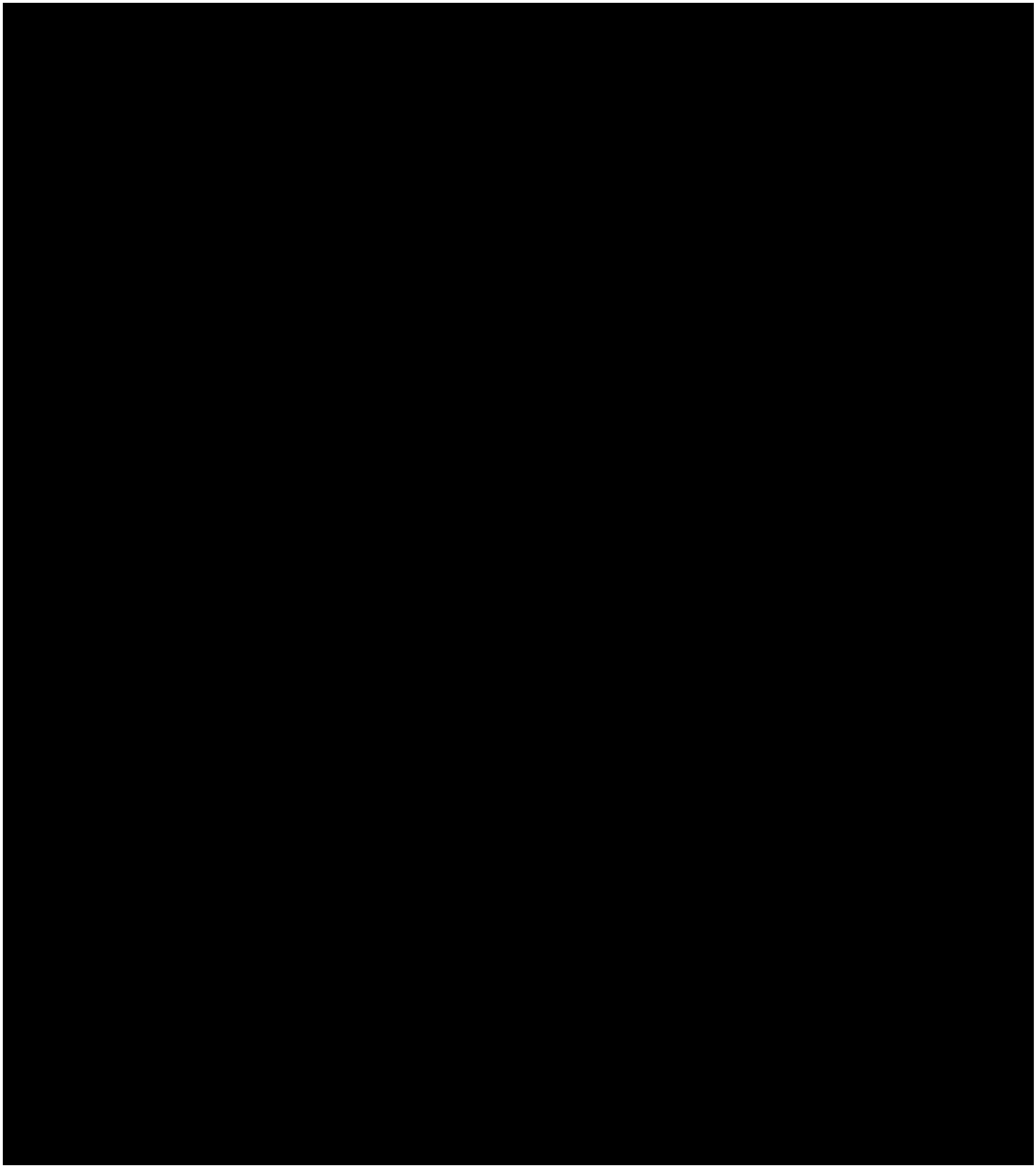

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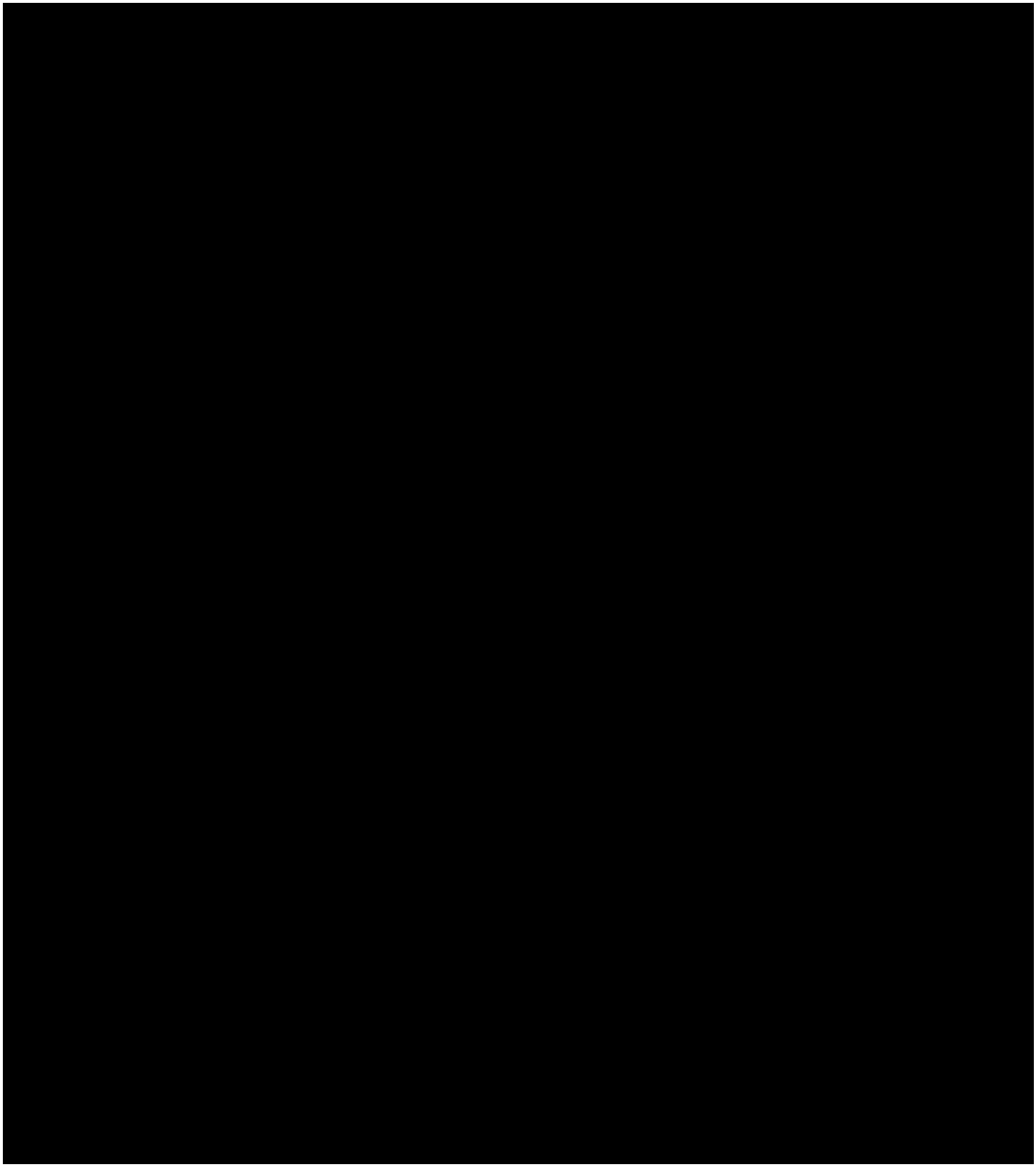

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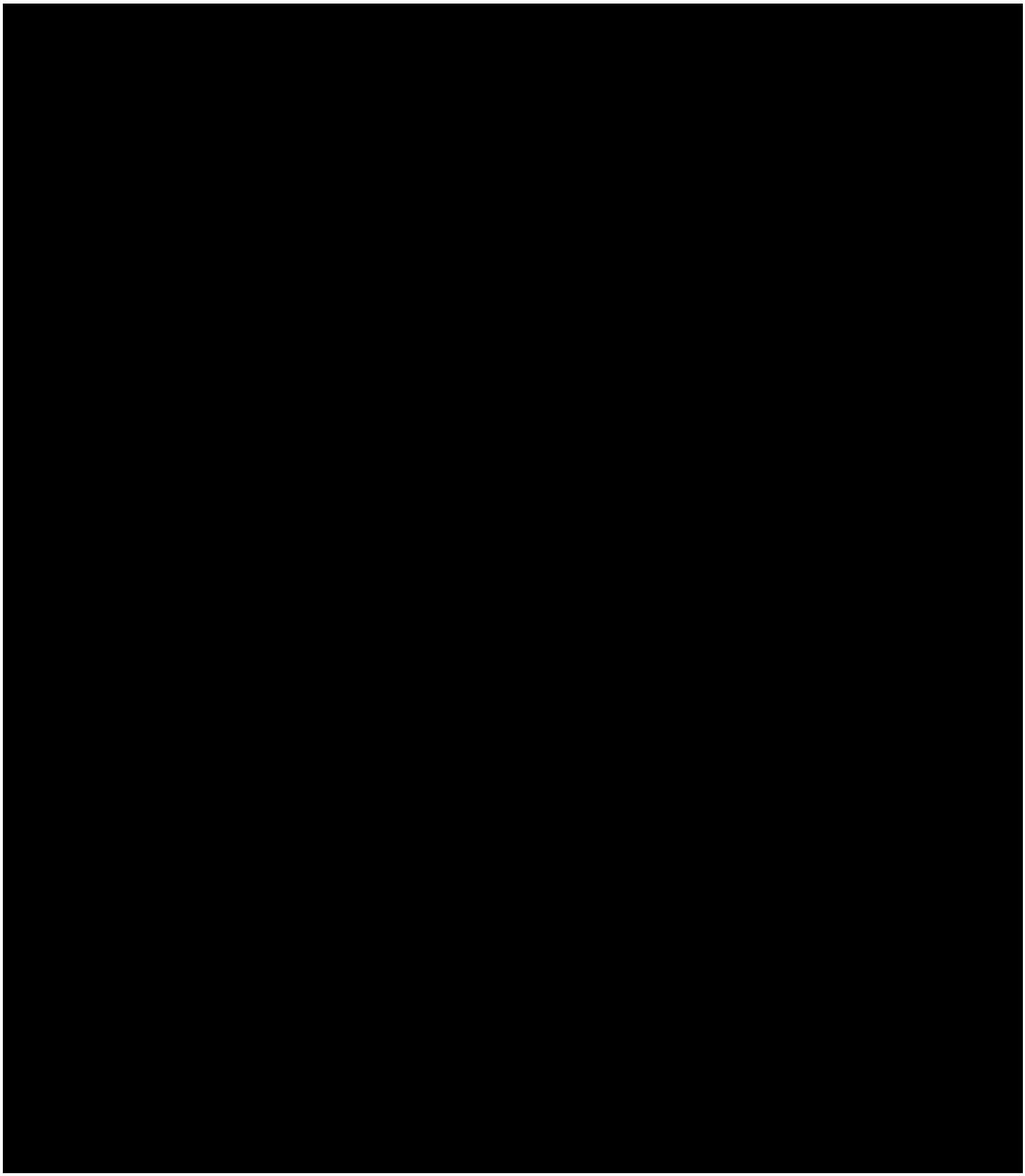

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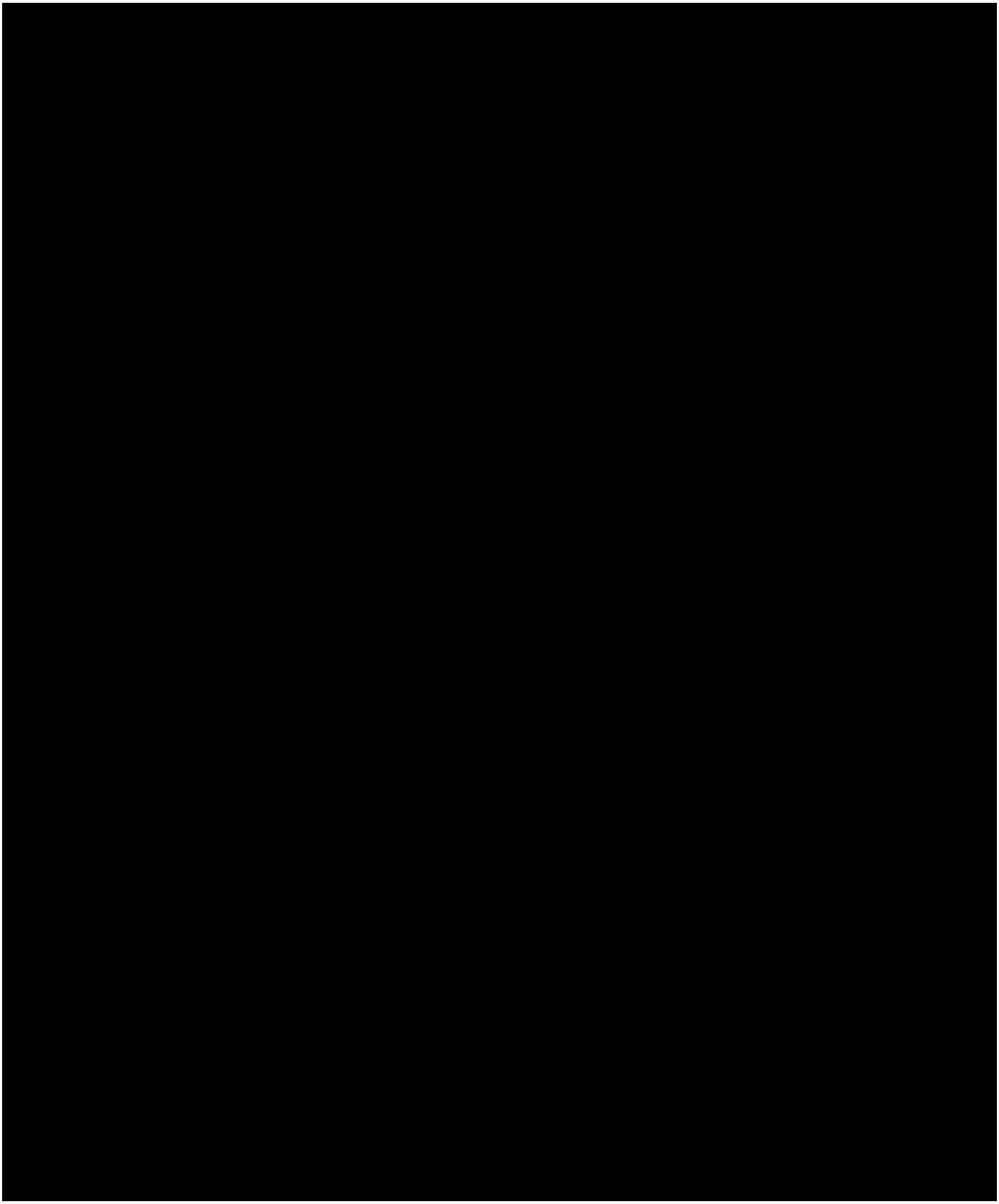

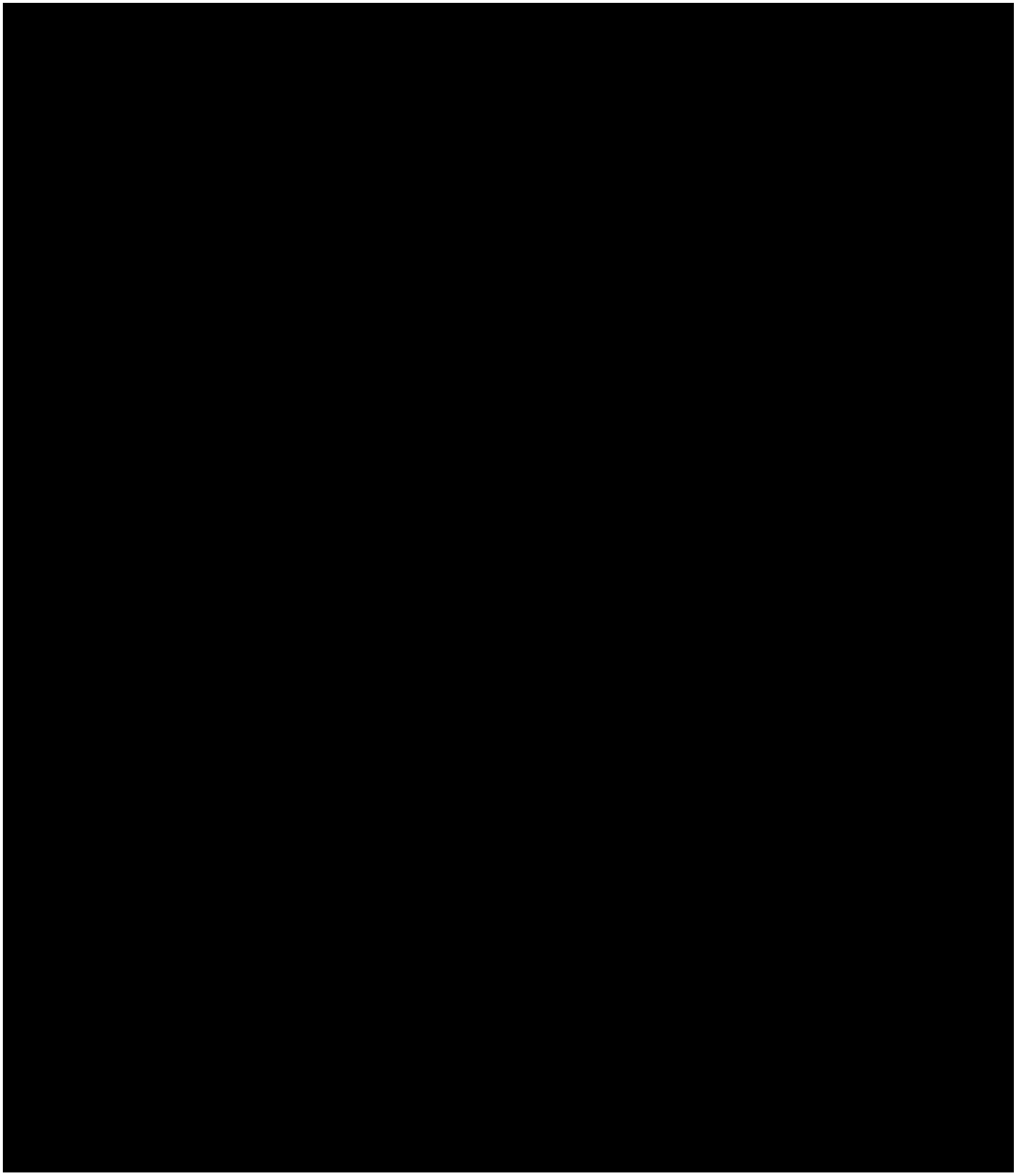

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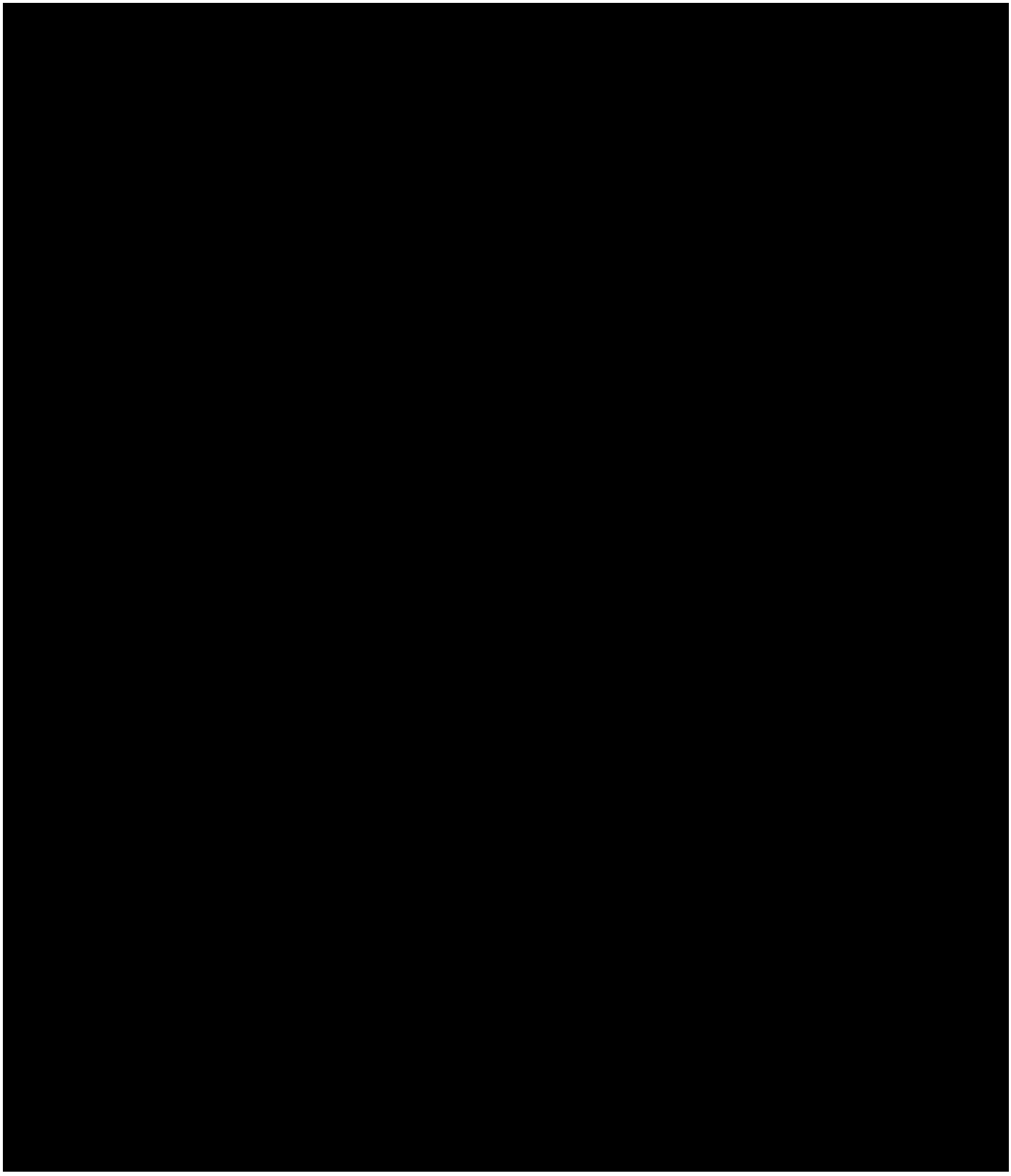

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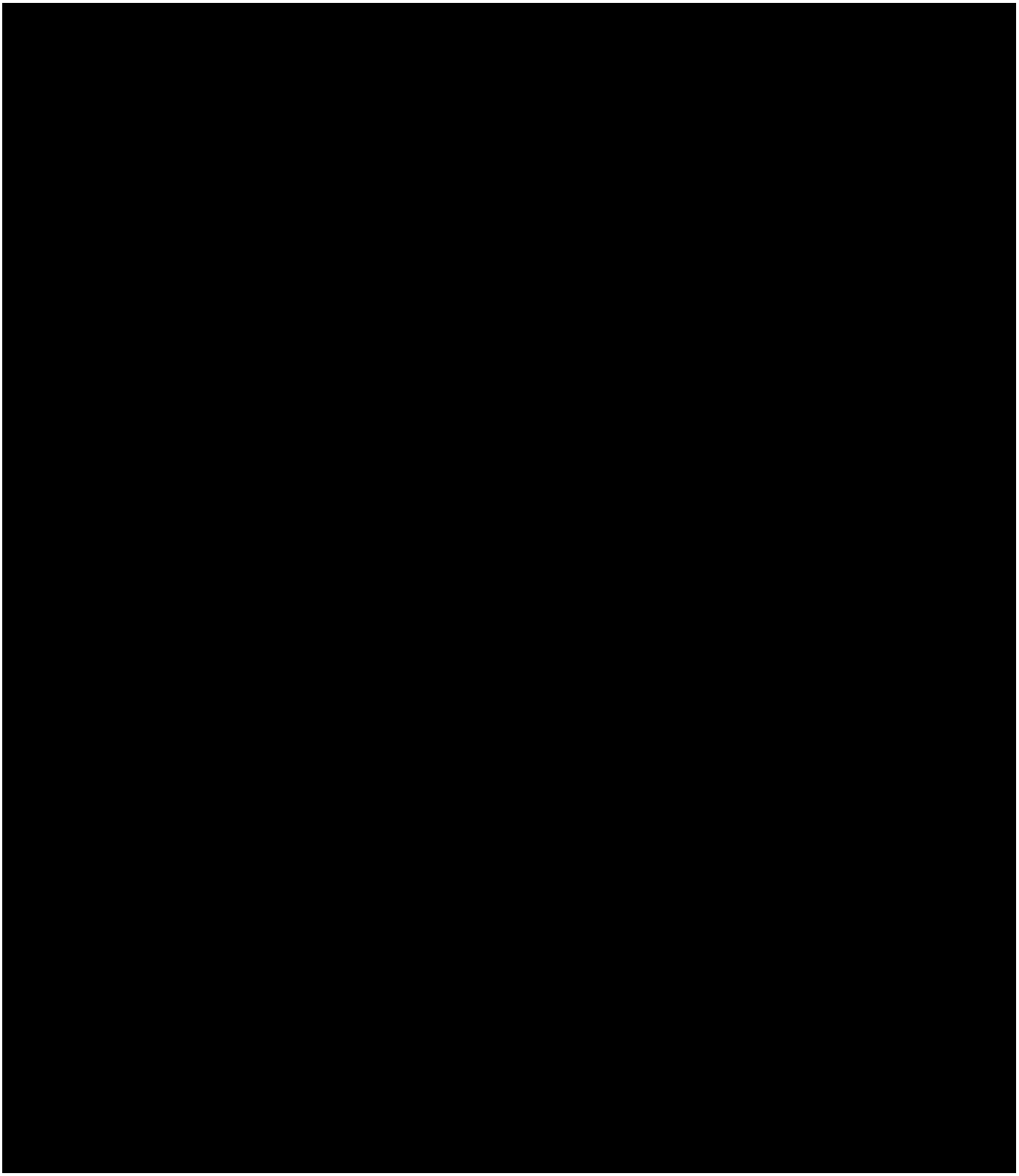

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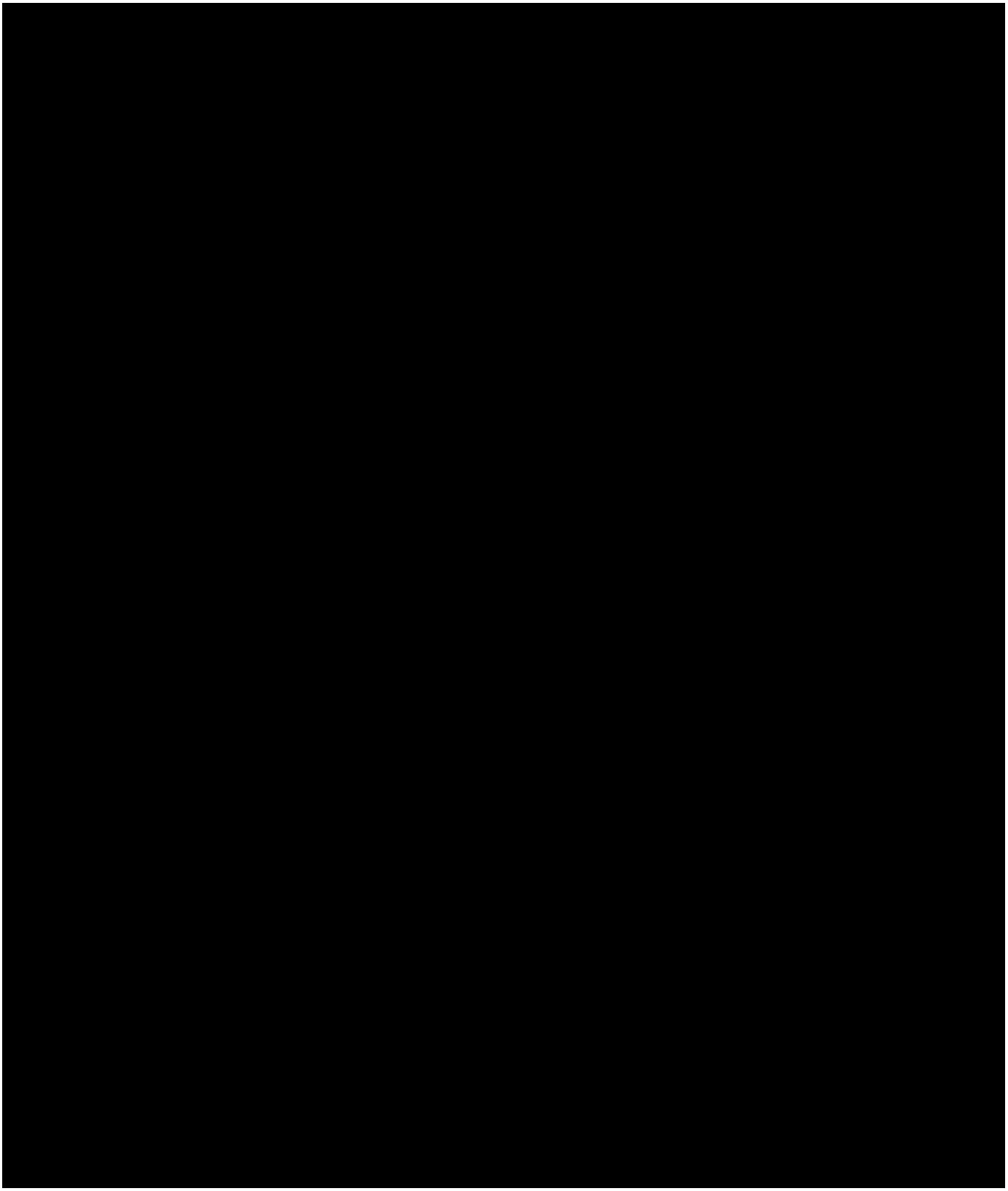

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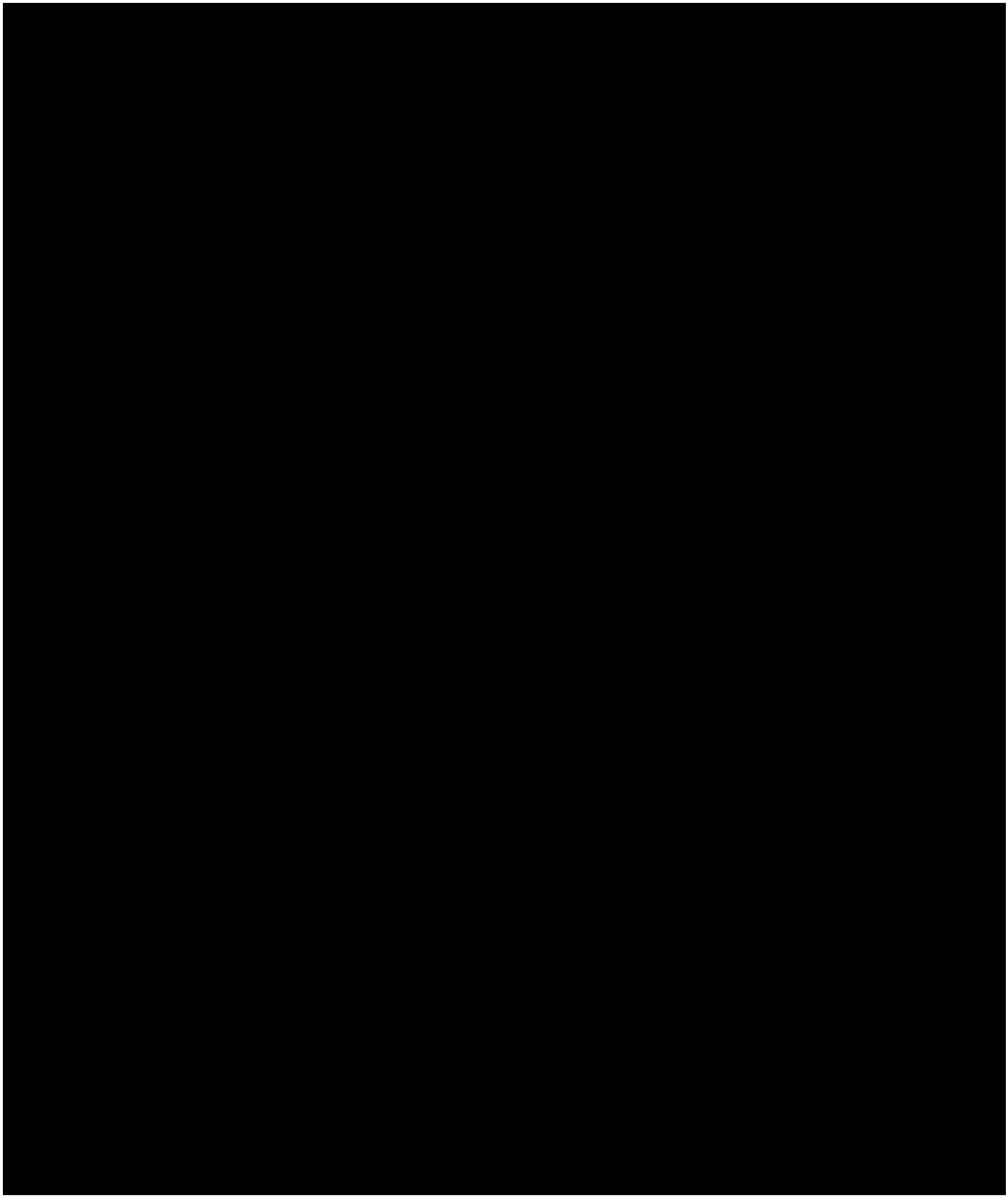

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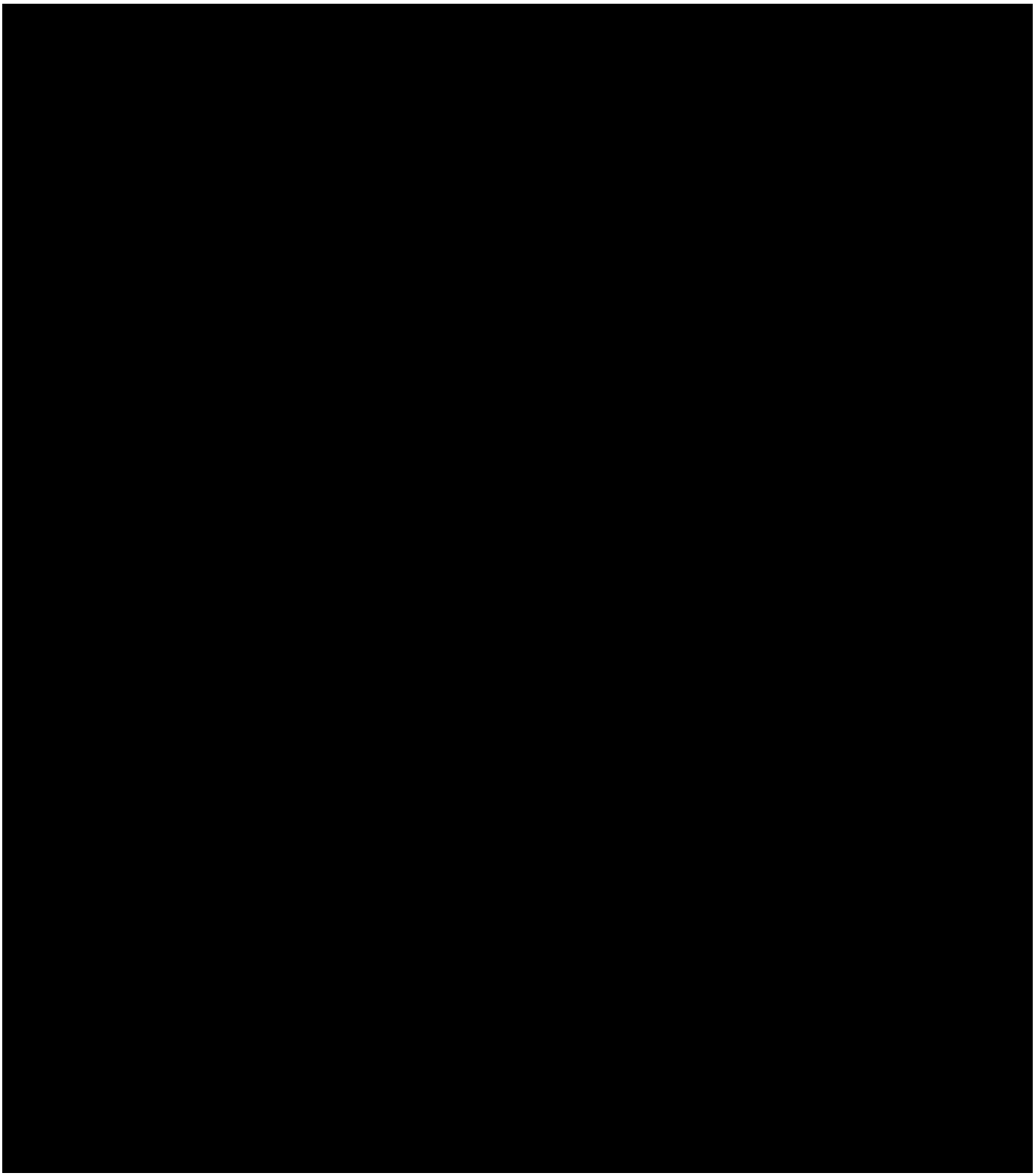

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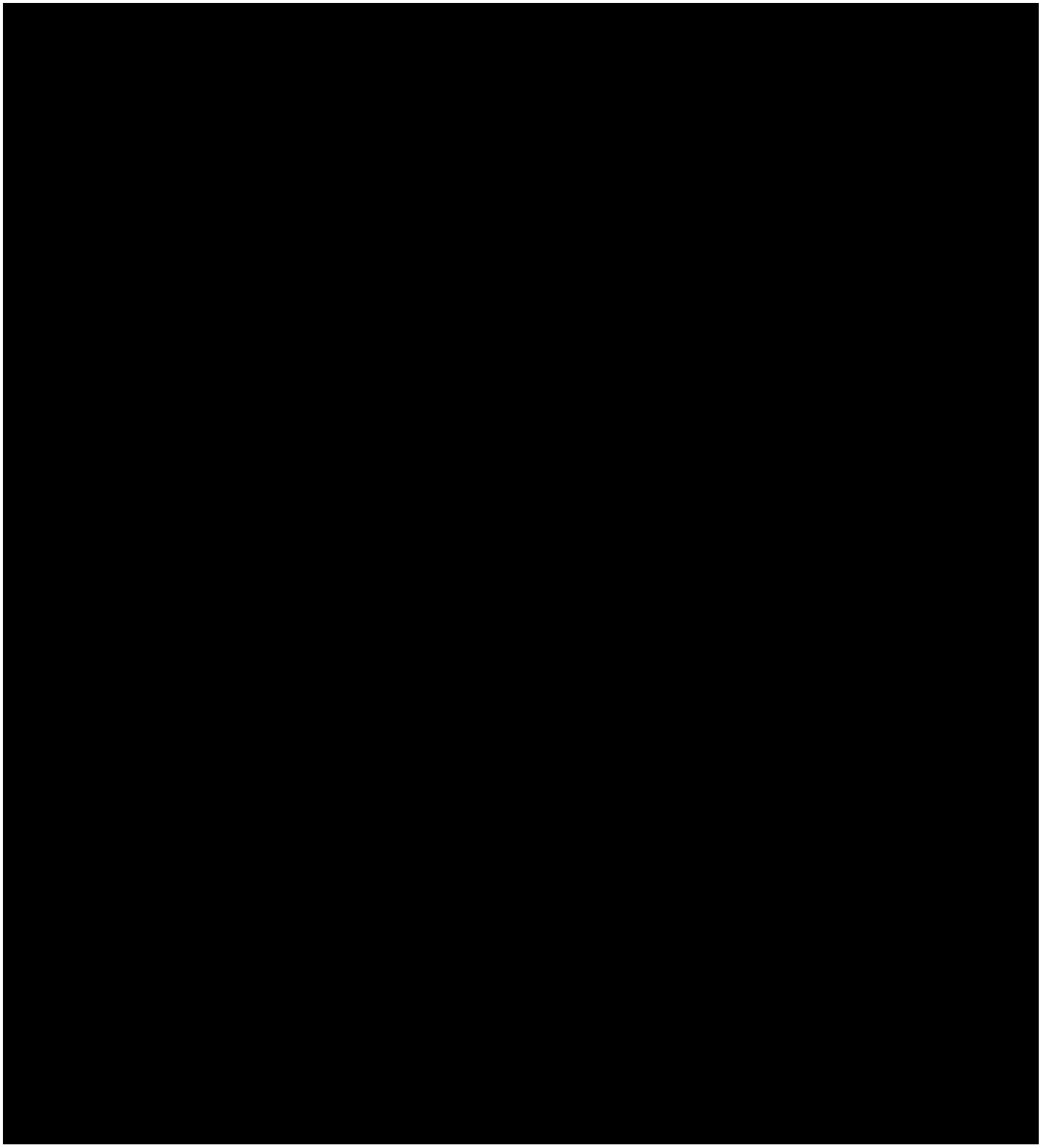

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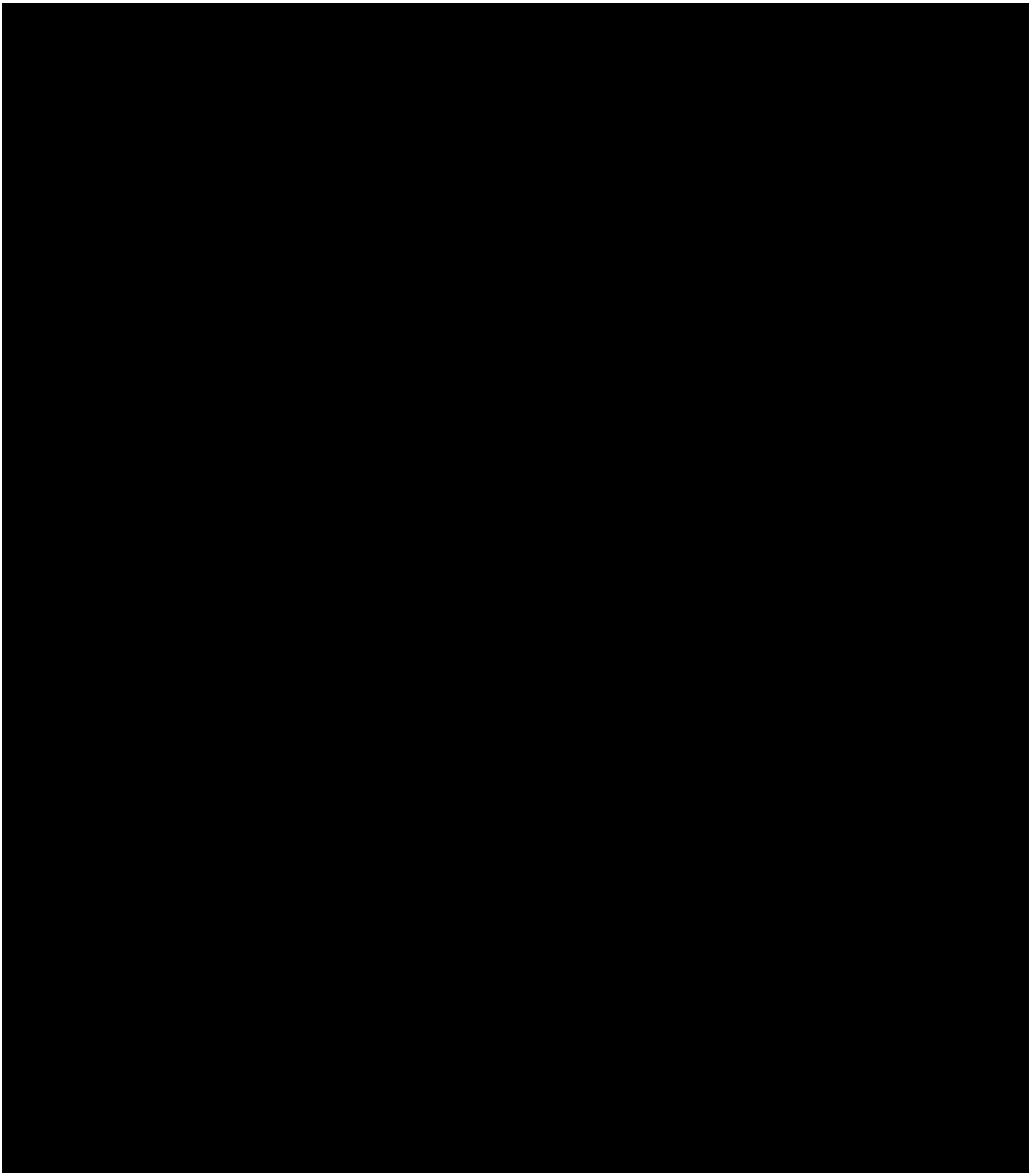

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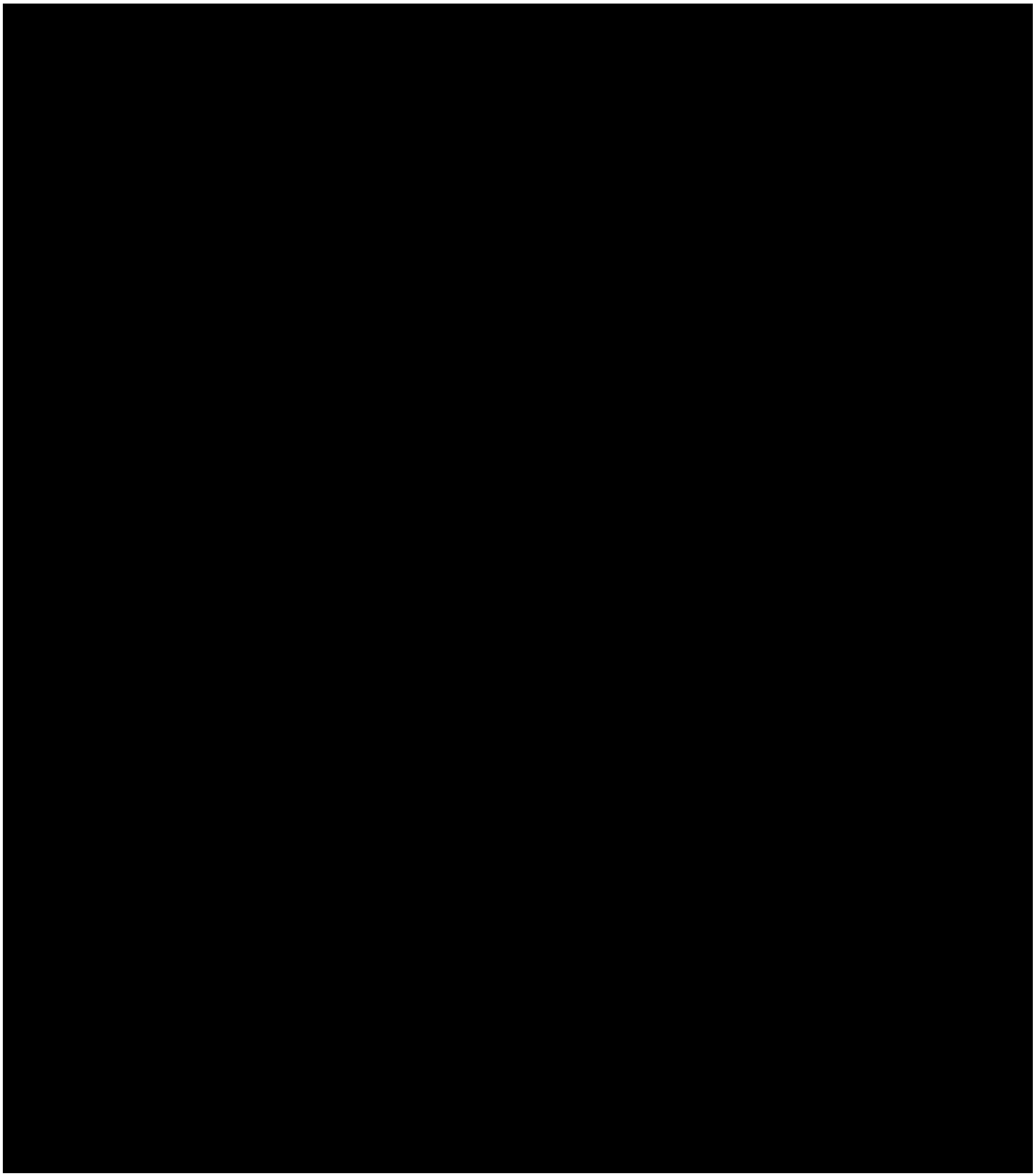

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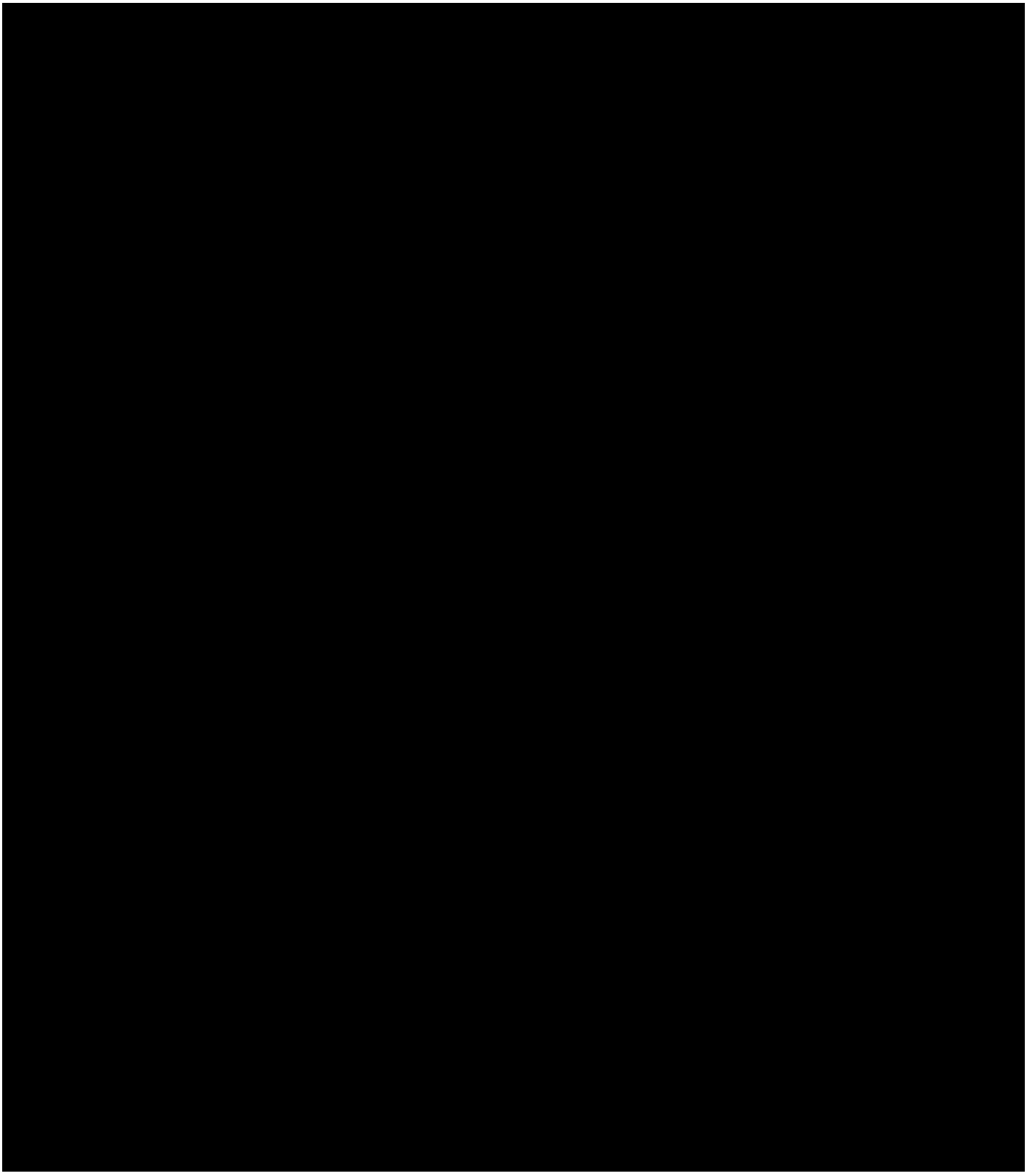

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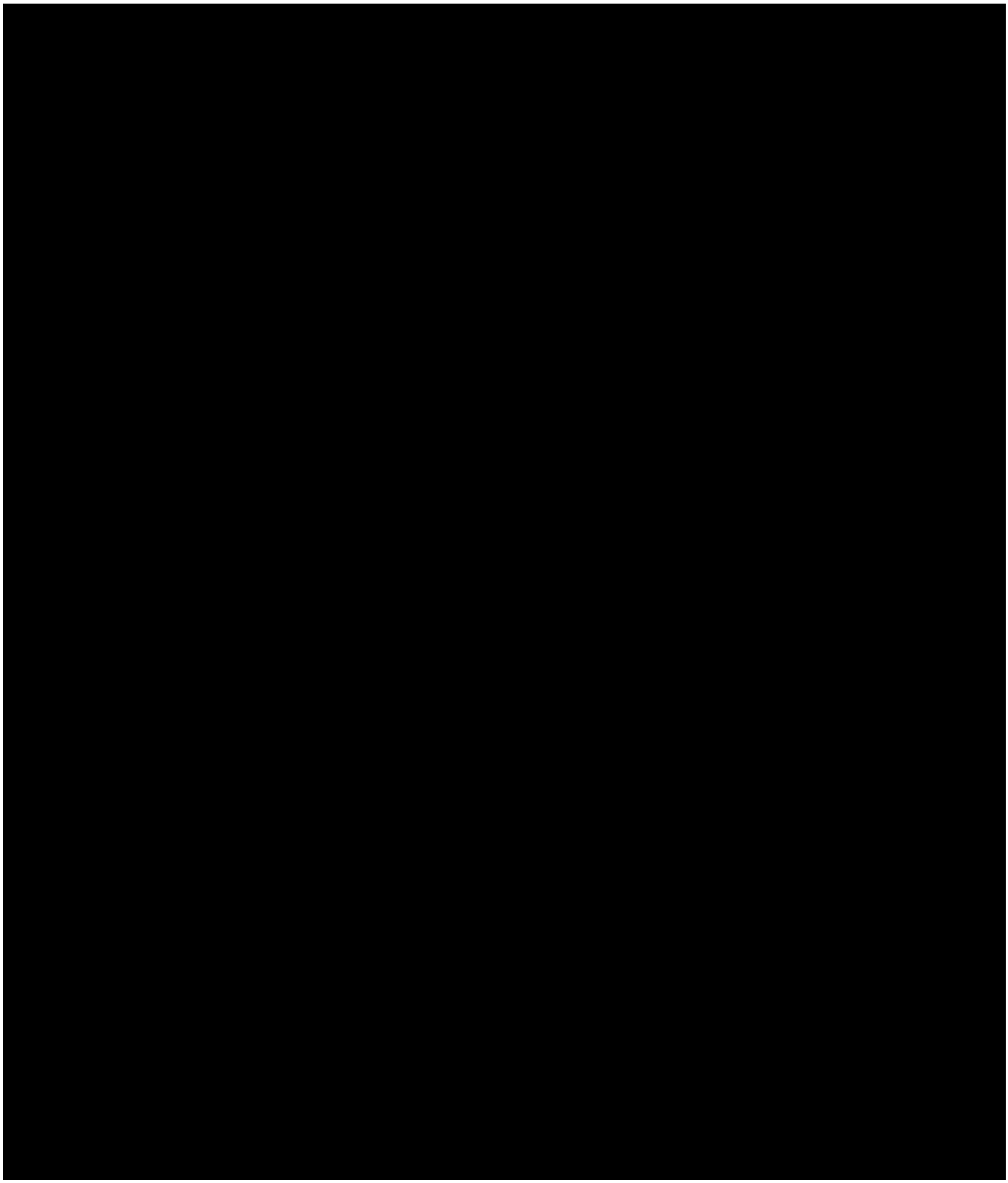

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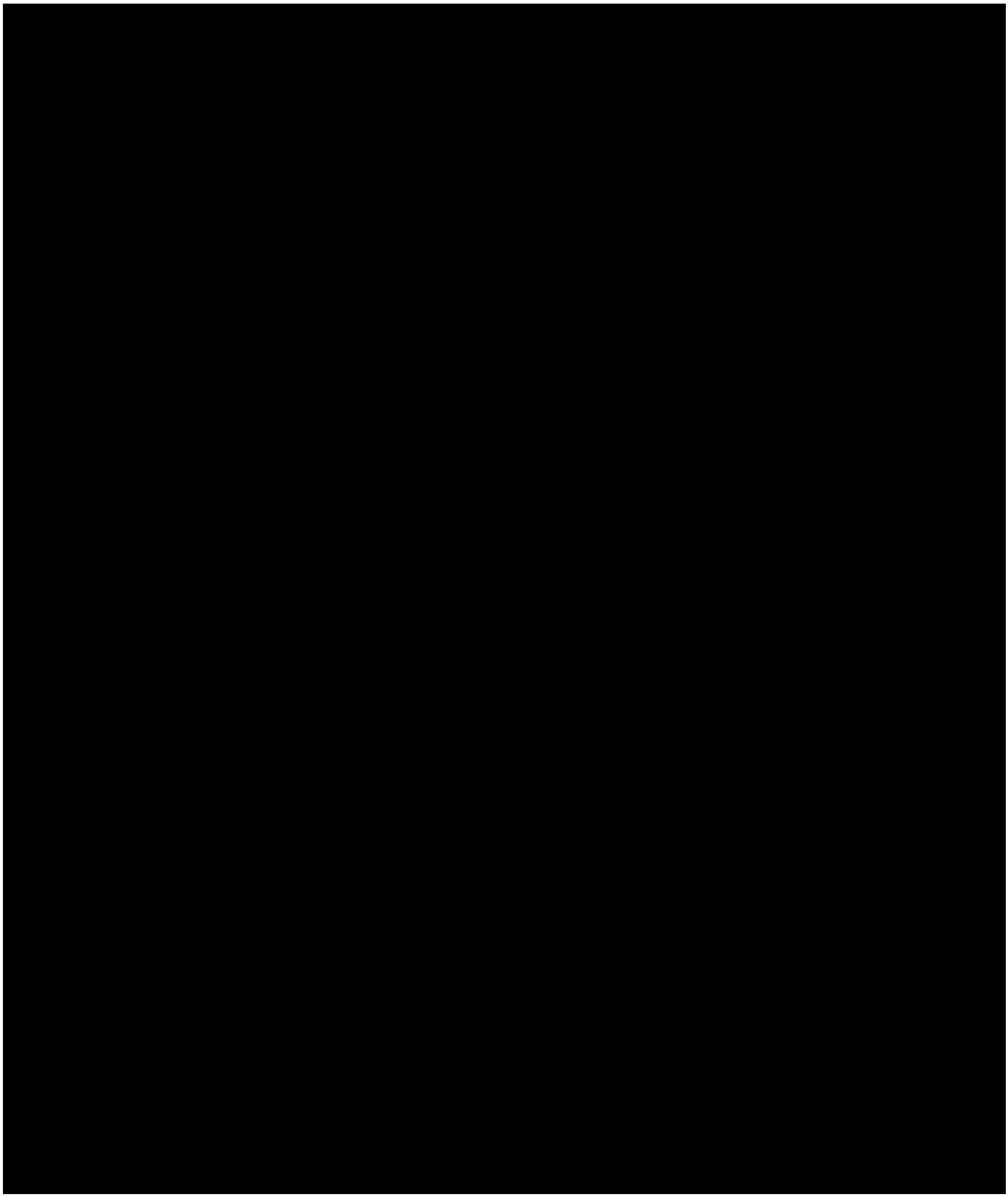

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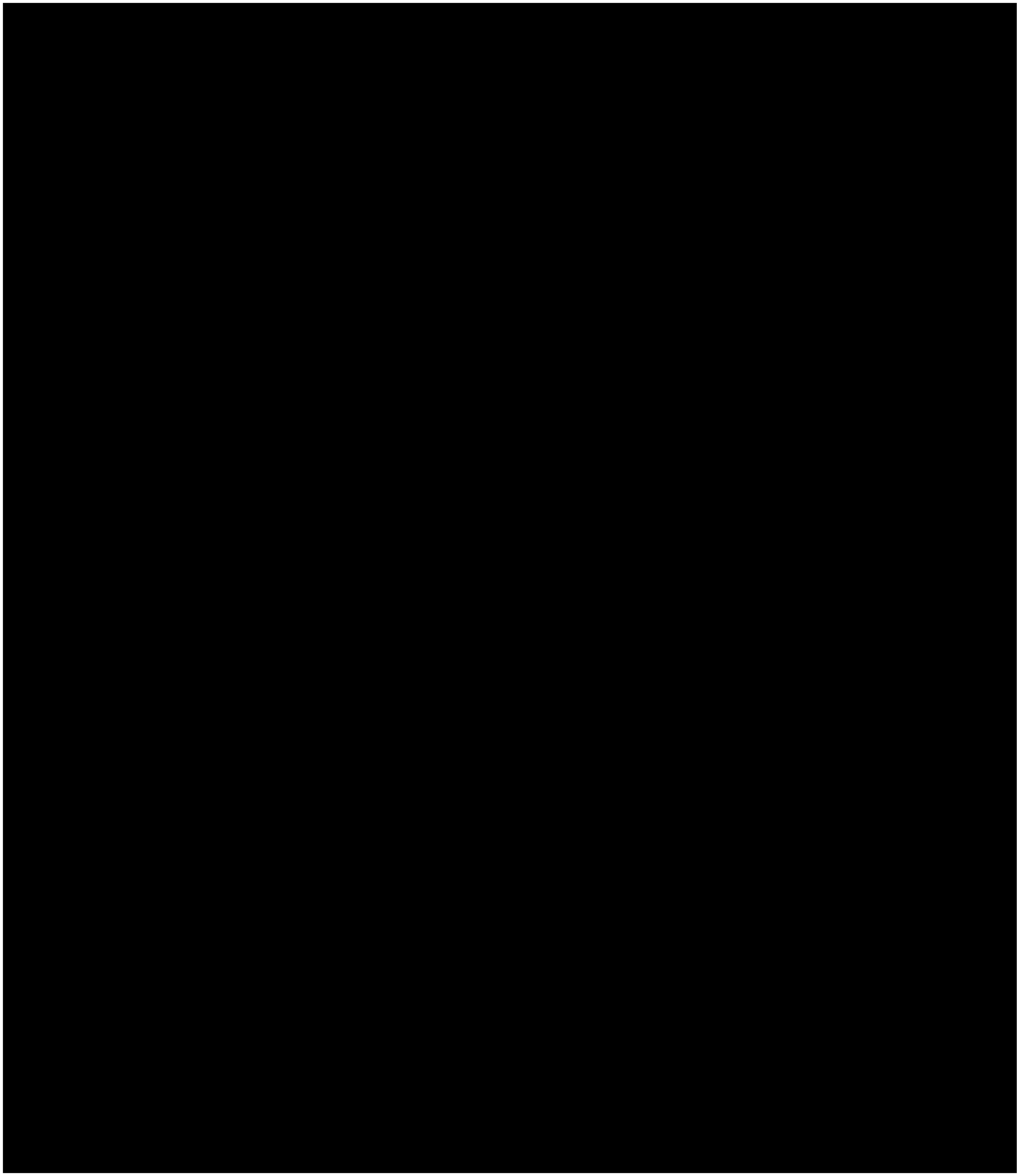

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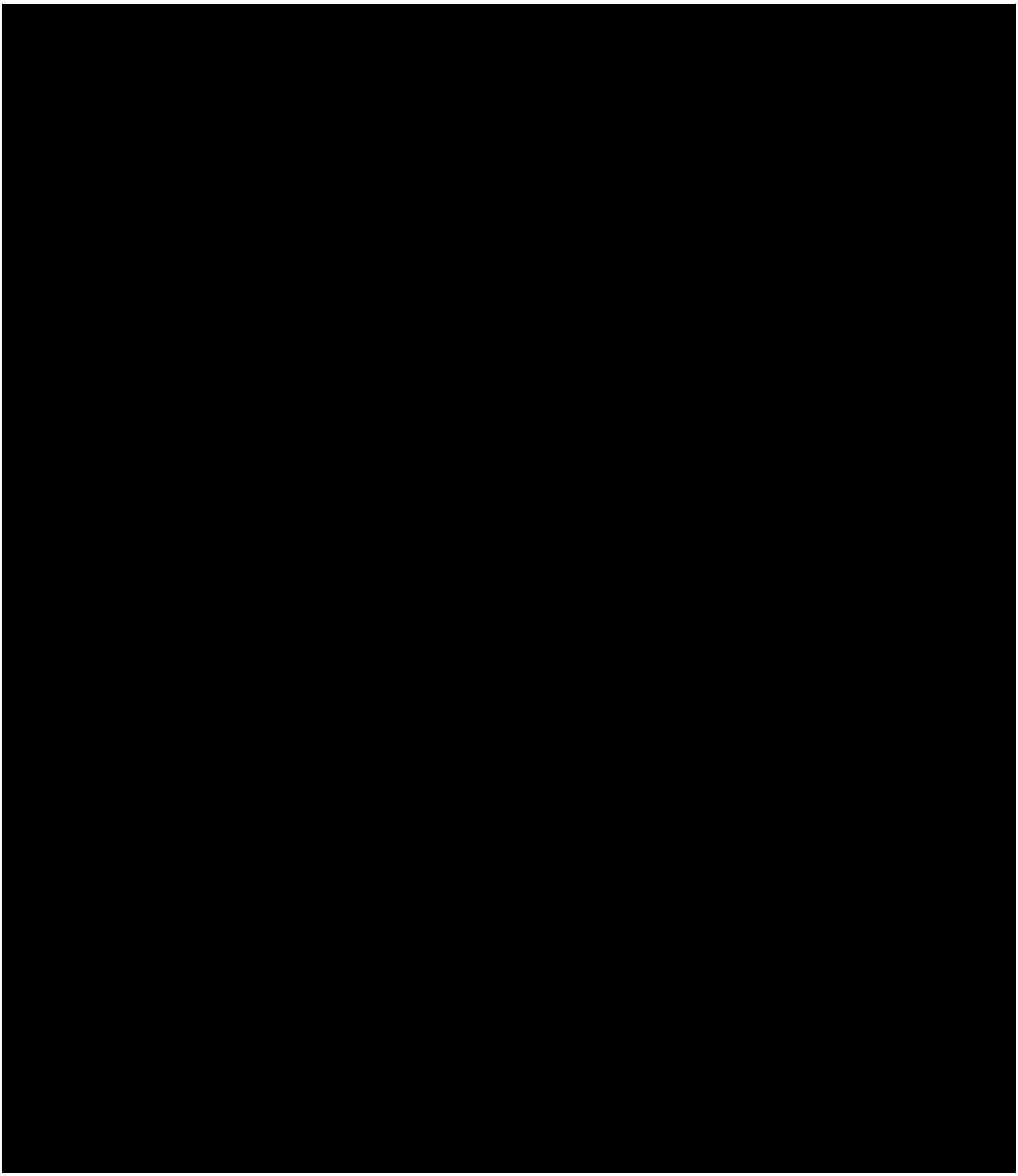

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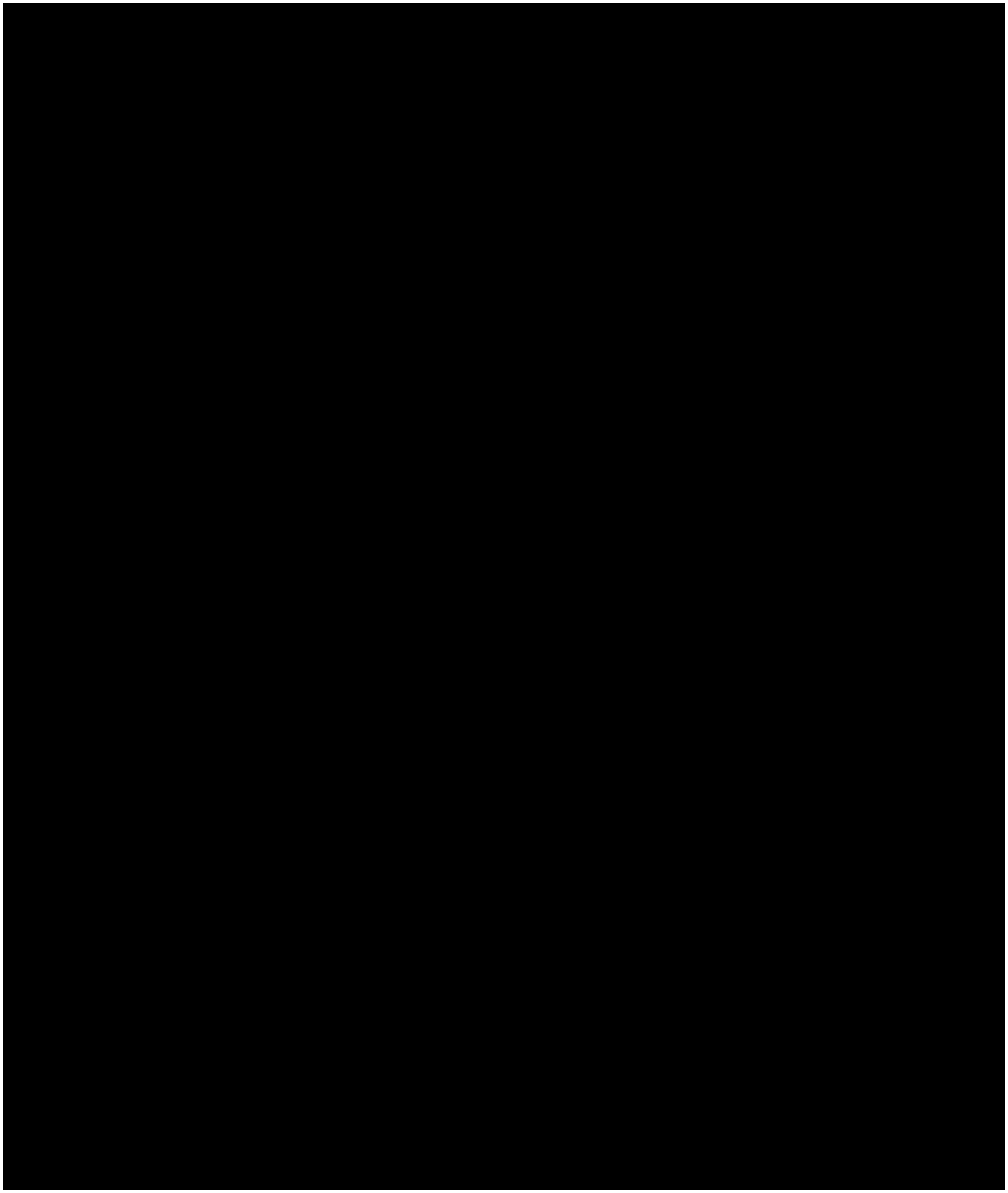

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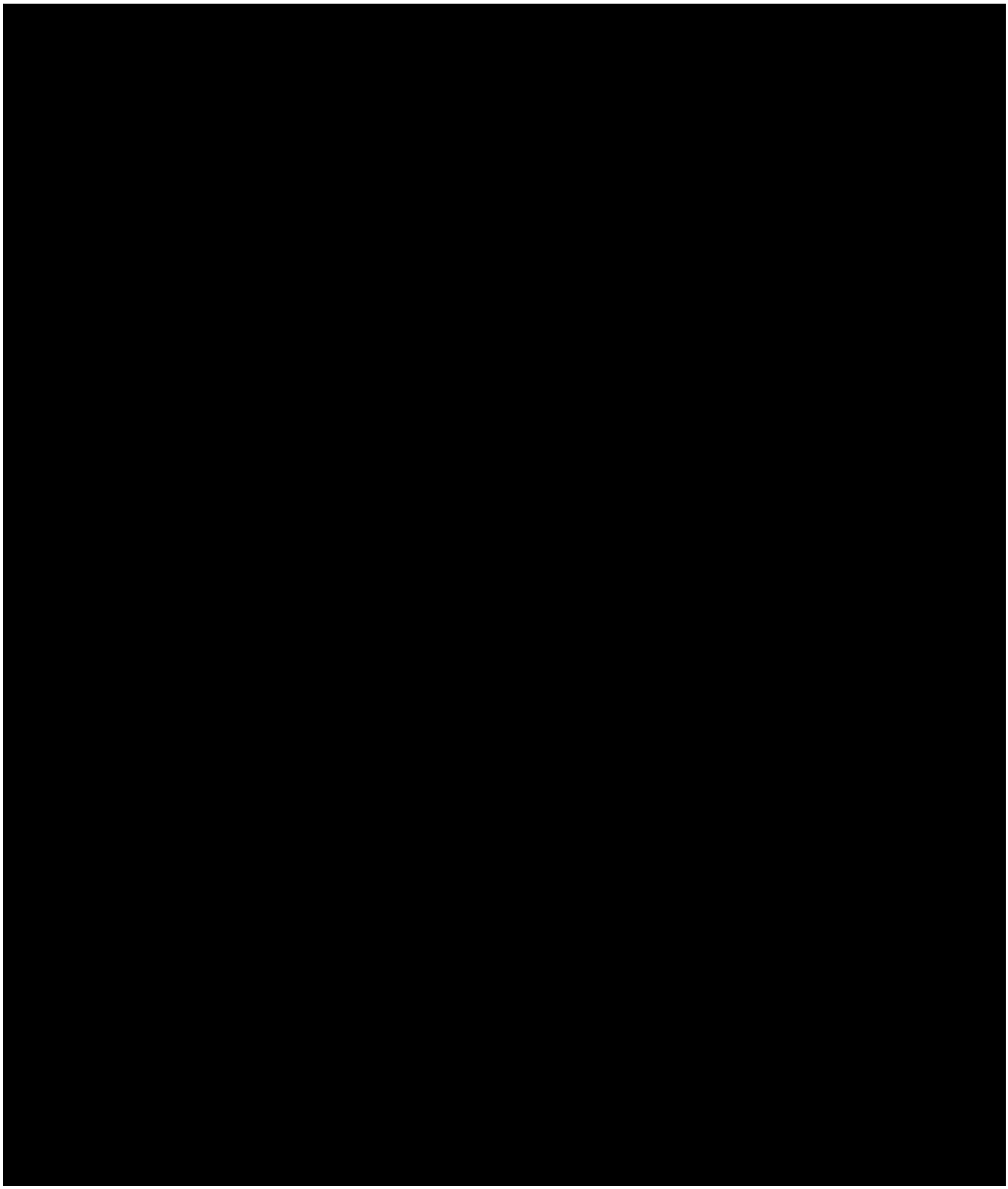

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