LOVELACE BIOMEDICAL

FINAL REPORT

14-Day Inhalation Toxicology Study in Male and Female Sprague Dawley Rats

Study Number:	FY19-149
Sponsor:	Canopy Growth USA LLC 1 Hershey Drive Smiths Falls, Ontario K7A 0A8
Test Facility:	Lovelace Biomedical 2425 Ridgecrest Drive, SE Albuquerque, NM 87108 Courier Address and Location of Laboratory: Bldg. 9217, Area Y Kirtland Air Force Base Albuquerque, NM 87115
Study Director:	[redacted] Lovelace Biomedical
Sponsor Representative:	[redacted] Canopy Growth

Study Initiation: 26Feb2020 **Study In-Life Completion:** 20Mar2020

STUDY DIRECTOR SIGNATURE

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Study Director Date

SPONSOR SIGNATURE

Sponsor Representative	Date

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LIST OF ACRONYMS/ABBREVIATIONS

µm	micrometer
°F	Degrees Fahrenheit
µg	microgram
AAALAC	Association for Assessment and Accreditation of Laboratory Animal Care
CFR	Code of Federal Regulations
DF	Deposition Fraction
FDA	Food and Drug Administration
g	Gram
GC-MS	Gas chromatrography-mass spectrometry
GSD	Geometric Standard Deviation
h	hour
kg	kilogram
L	Liter
LRRI	Lovelace Respiratory Research Institute
mg	milligram
Min	Minutes
mL	milliliter
MMAD	Mass median Aerodynamic Diameter
n/a	Not Applicable
PG	Propylene glycol
PSD	Particle size distribution
SOPs	Standard Operation Procedures
TA	Test article

EXECUTIVE SUMMARY

The primary objective of this study was to evaluate and compare the potential toxicity of two vaporized test materials (Phytol and Propylene Glycol (PG)) when administered to Sprague Dawley rats via nose-only inhalation at different dose levels.

Animals were exposed to filtered air or TA for up to 6 hours via nose-only inhalation for 14 consecutive days (air and PG only). Phytol exposures were discontinued and surviving animals were euthanized after 2 days of exposure due to animal mortality. Clinical observations, and body weights were recorded throughout the study. Tissues were harvested for histopathology, and blood was collected for clinical pathology.

Exposure to Phytol concentrations of 5.935 mg/L and 5.059 mg/L (Day 1 and Day 2, respectively) and presented/deposited doses of up to 1549.8/155.0 mg/kg with average particle sizes of 0.99 µm resulted in acute toxicity in all dose groups. Body weight loss and severe dose-dependent clinical signs (e.g. piloerection, hunched posture, rapid respiration) were observed starting on the first day of exposure and resulting in moribund euthanasia and death of all 4h and 6h within the first two days. All remaining Phytol dosed animals showed similar signs with progressing severity. Gross necropsy revealed discoloration of the lungs with dose-dependent increasing severity. Gross necropsy revealed discoloration of the lungs and increased lung weights. Microscopic evaluation resulted in prominent dose dependent adverse changes in the respiratory tract, with epithelial necrosis and loss of the upper respiratory tract and alveolar edema with fibrin, mixed alveolar inflammation, and hemorrhage in the lung. No NOAEL could be determined for Phytol based on the current study design. The LOAEL for inhalation administration is considered ≤ 109.0 / 10.9 mg/kg/day presented/deposited dose.

Exposure to PG concentrations of 4.427 mg/L and presented/deposited doses of up to 1151.7/115.2 mg/kg with average particle sizes of 2.05 µm over 14 days resulted in clinical signs including pilorection, hyperactivity and rapid respiration. However, all animals recovered until the following exposure day. No TA related changes in body weights gross pathology or clinical pathology parameters were detected. All microscopic findings were considered non-adverse. The NOAEL for PG inhalation in rats after 14 day exposure is considered 1151.7/115.2 mg/kg (presented/deposited dose).

1 OBJECTIVE

The primary objective of this study was to evaluate and compare the potential toxicity of two vaporized test materials (Phytol and Propylene Glycol) when administered to Sprague Dawley rats via nose-only inhalation at different dose levels. [redacted]

2 COMPLIANCE

[redacted]

This study complies with all applicable sections of the Final Rules of the Animal Welfare Act regulations (9 CFR Parts 1, 2, and 3), as well as the *Guide for the Care and Use of Laboratory Animals* (2011). Lovelace Biomedical (LRRI) is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).

3 KEY STUDY PERSONNEL

Study Director: [redacted]

Sponsor Representative: [redacted]

Program Oversight: [redacted]

Contributing Scientist – Aerosol: [redacted]

Contributing Scientist – Chemistry: [redacted]

Contributing Scientist – Pathology: [redacted]

Attending Veterinarian: [redacted]

[redacted]

4 TEST ARTICLE

The test article (TA) certificates of analysis are provided in Appendix B.

4.1 Phytol

Identity: Phytol (EX00018- Vape Diluent Phytol 95% P-2000)

Description: Colorless to pale yellow liquid

Supplier/Manufacturer: Penta Manufacturing

Stability/Storage Conditions: Stored in a tightly closed container in a dry and well-ventilated place

4.2 Propylene Glycol

Identity: Propylene Glycol (PG)

Description: Colorless liquid

Supplier/Manufacturer: Huntsman

Stability/Storage Conditions: Stored at less than 100°F in its factory packaged container

5 METHODS

[redacted]

The experimental design is outlined in Table 1. Animals (5M/5F per group) were exposed to filtered air or a target aerosol concentration of 5 mg/L PG at different durations via nose-only inhalation for 14 consecutive days. Clinical observations, and body weights were recorded. Animals were euthanized on the day following their last exposure (24 ± 2 hours). Tissues were harvested for histopathology, and blood was collected for clinical pathology. Phytol exposures (target aerosol concentration of 5 mg/L) were discontinued after 2 days of exposure due to animal mortality. Surviving animals were euthanized. Gross necropsy and tissue preservation was performed.

Table 1. Experimental Design

Group	Treatment	Target Aerosol Concentration (mg/L)	Exposure Duration (h)	Estimated Presented / Deposited Dose (mg/kg)*	Animals	
					Male	Female

[redacted]

6 RESULTS

6.1 Inhalation Exposure and Pulmonary Doses

Table 2 shows a summary of the aerosol analysis of the Phytol exposure atmosphere. The average Phytol concentration was 5.935 mg/L and 5.059 mg/L on Day 1 and Day 2, respectively, resulting in estimated presented/deposited dose ranges of 129.5/12.9 to 1549.8/155.0 for 0.5 to 6 h exposure duration on Day 1. Day 2 exposures resulted in estimated presented/deposited doses of 110.4/11.0 mg/kg for 0.5 h exposures, 219.8/22.0 mg/kg for 1 h exposures, and 441.5/44.1 mg/kg for 2 h exposures. High doses (4 and 6 h exposure duration) were discontinued after Day 1.

Table 3 shows a summary of the aerosol analysis of the PG exposure atmosphere. The average PG concentration was 4.427 mg/L, resulting in estimated presented/deposited dose ranges of 95.6/9.6 to 1151.7/115.2 for 0.5 to 6 h exposure duration.

The mass median aerodynamic diameter (MMAD) averaged 0.99 and 2.05 µm for Phytol and PG, respectively.

Detailed results on exposure atmosphere characterization are presented in the Aerosol Contributing Scientist Report in Appendix D.

Table 2. Phytol Daily Dose Summary

Group	Exposure Duration (h)	Day 1				Day 2			
		Average Gravimetric Conc. (mg/L)	Average API Conc. (mg/L)	Presented Dose (mg/kg)	Deposited Dose (mg/kg)	Average Gravimetric Conc. (mg/L)	Average API Conc. (mg/L)	Presented Dose (mg/kg)	Deposited Dose (mg/kg)
[redacted]	0.5	[redacted]	5.935	129.5	12.9	[redacted]	5.059	110.4	11.0
	1			257.9	25.8			219.8	22.0
	2			517.9	51.8			441.5	44.1

5	4			1033.2	103.3			NA	NA
6	6			1549.8	155.0			NA	NA

Table 3. Propylene Glycol Daily Dose Summary

Group	Exposure Duration (h)	Average Gravimetric Conc. (mg/L)	Average API Conc. (mg/L)	Presented Dose (mg/kg)	Deposited Dose (mg/kg)
7	0.5	[redacted]		95.6	9.6
8	1			191.2	19.1
9	2			382.5	38.3
10	4			765.3	76.5
11	6			1151.7	115.2

6.2 Clinical Observations and Survival

Phytol group animals expressed severe TA related clinical signs (e.g. piloerection, hunched posture, rapid respiration) starting on the first day of exposure and resulting in moribund euthanasia and death within the first two days. PG exposed animals occasionally presented piloerection, hyperactivity, or rapid respiration post exposure. All animals recovered before the next exposure. A summary is provided in Table 4.

On Day 1, three Phytol 4 h animals (2 male, 1 female) and three Phytol 6 h animals (3 male) were found dead. A male Phytol 4 h and a male Phytol 6 h animal were euthanized moribund on Day 1. On Day 2, three Phytol 4 h animals (2 male, 1 female) and three Phytol 6 h animals (1 male, 2 females) were found dead. After discussion with the sponsor, all remaining Phytol dosed animals were euthanized on Day 2. A detailed list of early deaths is shown in Table 5.

Individual animal clinical observations are included in Appendix F.

Table 4. Summary of Clinical Observations

Group	Exposure duration (h)	Findings
Air	6	no findings on any of the 14 exposure days
Phytol	0.5	Day 2 moribund euthanasia n=10 (post Day 2 exposure) other findings: Piloerection, hunched posture, rapid respiration
	1	Day 2 moribund euthanasia n=10 (post Day 2 exposure) other findings: Piloerection, hunched posture, rapid respiration
	2	Day 2 moribund euthanasia n=10 (post Day 2 exposure) other findings: Piloerection, hunched posture, rapid respiration
	4	Day 1 moribund euthanasia n=1, Day 2 moribund euthanasia n=3, Day 1 found dead n=3, Day 2 found dead n=3 other findings: Lethargy, piloerection, hunched posture, nasal discharge, labored respiration, rapid respiration, open mouth breath

	6	Day 1 moribund euthanasia n=1, Day 2 moribund euthanasia n=3, Day 1 found dead n=3, Day 2 found dead n=3 other findings: Ataxia, lethargy, piloerection, hunched posture, nasal discharge, labored respiration, rapid respiration
PG	0.5	Piloerection, hyperactive starting day 4
	1	Piloerection, hyperactive starting day 4
	2	Piloerection, hyperactive starting day 4
	4	Piloerection, hyperactive starting day 4; rapid respiration in 1-2 individuals on Day 1 to 4
	6	Piloerection, hyperactive starting day 4

Table 5. Summary of Early Deaths

Study Day 1 Disposition		Study Day 2 Disposition	
Animal ID	**Disposition**	**Animal ID**	**Disposition**
5001	Found Dead	2001-2010	Moribund
5003	Found Dead	3001-3010	Moribund
5004	Moribund	4001-4010	Moribund
5007	Found Dead	5002	Found Dead
6001	Moribund	5005	Found Dead
6002	Found Dead	5006	Moribund
6003	Found Dead	5008	Moribund
6005	Found Dead	5009	Found Dead
		5010	Moribund
		6004	Found Dead
		6006	Found Dead
		6007	Moribund
		6008	Found Dead
		6009	Moribund
		6010	Moribund

6.3 Bodyweights

Body weights per group and gender are shown in Figure 1. Similar to the air control, body weights of PG exposed male animals increased throughout the duration of the study. Female animal body weights of air control and PG exposed animals remained consistent. Body weights of male and female animals exposed to Phytol decreased within from exposure start to termination on Day 2. Individual animal data is included in Appendix G.

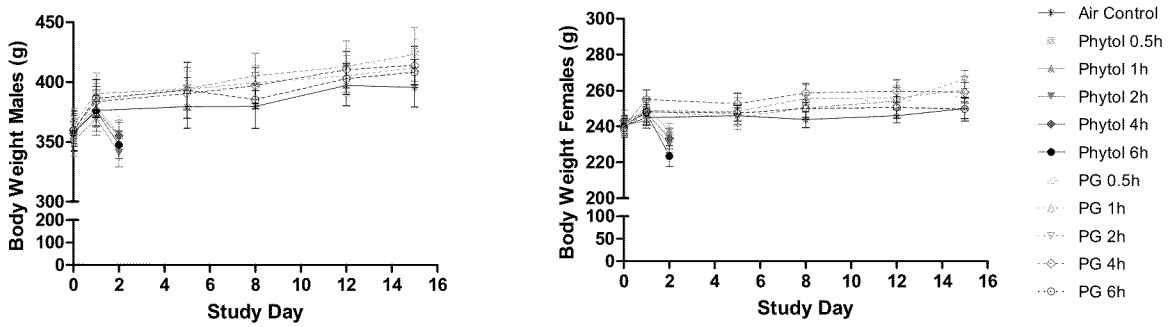

Figure 1. Body Weights.

Day 0 values present pre exposure body weight collected on Day -3 or -4.

6.4 Pathology

6.4.1 Gross Pathology

Phytol 4h and 6h animals all demonstrated severely discolored purple lungs on gross examination. The lower dose groups demonstrated variable degrees of dark red discoloration varying from patchy to small multiple, punctate areas. Air Control and Propylene Glycol groups were grossly unremarkable. Individual animal gross pathology data is included in Appendix G. Air control and PG exposed animals did not show any visible lesions at necropsy. A majority of Phytol animals were noted to have dark red discoloration on the lungs.

6.4.2 Organ Weights

Individual organ weights are included in Appendix G, and group averages are summarized in Table 6. A dose responsive increase was present in available lung weights and lung to body weight ratio for all Phytol groups, with Group 6 lung weight increased over 4 fold that of Air controls. Lung weights of Propylene Glycol exposed animals were unremarkable versus Air controls.

Table 6. Summary of Organ Weights

Male											
Parameter	Air Control	Phytol					PG				
		0.5h	1h	2h	4h	6h	0.5h	1h	2h	4h	6h
Adrenals	0.056	-	-	-	-	-	0.077	0.061	0.058	0.068	0.065
Brain	2.10	-	-	-	-	-	2.12	2.14	2.11	2.09	2.09
Epididymides	1.28	-	-	-	-	-	1.39	1.46	1.36	1.35	1.57
Heart	1.27	-	-	-	-	-	1.31	1.24	1.35	1.34	1.25
Kidneys	2.41	-	-	-	-	-	2.48	2.59	2.55	2.48	2.50
Liver	14.5	-	-	-	-	-	15.3	15.3	14.8	14.7	13.6
Lungs	1.74	1.94	2.15	2.27	**5.45**[a]	**7.33**	1.80	1.67	1.75	1.90	1.80
Spleen	0.768	-	-	-	-	-	0.713	0.722	0.758	0.852	0.848
Testes	3.34	-	-	-	-	-	3.43	3.35	3.38	3.32	3.39
Thymus	0.429	-	-	-	-	-	0.429	0.473	0.457	0.528	0.494
Female											
Parameter	Air Control	Phytol					PG				
		0.5h	1h	2h	4h	6h	0.5h	1h	2h	4h	6h

Adrenals	0.0628	-	-	-	-	-	0.0618	0.0696	0.0608	0.0852	0.0696
Brain	1.90	-	-	-	-	-	2.01	1.92	1.98	1.89	1.89
Heart	0.837	-	-	-	-	-	0.860	0.848	0.860	0.829	0.834
Kidneys	1.52	-	-	-	-	-	1.50	1.54	1.54	1.52	1.47
Liver	9.13	-	-	-	-	-	8.85	9.47	8.95	9.25	8.59
Lungs	1.37	1.45	1.59	1.82	**2.78**	**2.92**	1.35	1.39	1.37	1.32	1.36
Ovaries	0.119	-	-	-	-	-	0.096	0.131	0.119	0.134	0.122
Spleen	0.552	-	-	-	-	-	0.541	0.524	0.549	0.500	0.557
Thymus	0.423	-	-	-	-	-	0.433	0.398	0.418	0.429	0.378
Uterus	0.531	-	-	-	-	-	0.524	0.585	0.581	0.524	0.556

[a] Bold values have a calculated percent change greater than 50% from Air Control.

6.4.3 Microscopic Observations

Phytol exposed groups demonstrated prominent changes within the respiratory tract after 1 (Groups 5, 6) or 2 (Groups 2-4) days of exposure. Prominent changes in early deaths (especially in Groups 5 and 6) included dose-responsive degeneration and necrosis of epithelium within the nose/turbinates (multiple levels), larynx, and trachea. In the lungs of these animals, the primary changes included pulmonary edema with fibrin, and widespread mixed cell inflammation with abundant macrophages, lymphocytes and neutrophils. Additional findings including hemorrhage and epithelial degeneration were also present in severely affected lungs.

For animals in Phytol groups 2, 3 and 4 there were less severe changes, although the mixed cell inflammation in the lungs was present in all animals and demonstrated a distinct centriacinar distribution. The findings in the nose, airways and lungs of all Phytol groups are considered adverse.

Animals exposed to Propylene Glycol were largely unremarkable, with only minor and inconsistent changes. In the larynx, minimal epithelial alteration characterized by flattening and slight increase in cell layers was occasionally present, and minimal increases in unremarkable alveolar macrophages were present in some animals. Both changes are well recognized, common findings in inhalation exposures. Both changes were sporadic, but slightly more frequent in animals in higher exposure duration groups. At the minimal to mild levels seen in this study, neither change is considered to be adverse.

Detailed results are provided in the Pathology Report (Appendix G).

[redacted]

7 CONCLUSION

Exposure to Phytol concentrations of 5.935 mg/L and 5.059 mg/L (Day 1 and Day 2, respectively) and presented/deposited doses of up to 1549.8/155.0 mg/kg resulted in body weight loss and severe dose-dependent clinical signs (e.g. piloerection, hunched posture, rapid respiration) starting on the

first day of exposure and resulting in moribund euthanasia and death of all 4h and 6h within the first two days. All remaining Phytol dosed animals showed similar signs with progressing severity. Therefore Phytol exposure was discontinued and all remaining animals were euthanized on Day 2. Gross necropsy revealed discoloration of the lungs and increased lung weights. Microscopic evaluation resulted in prominent dose dependent adverse changes in the respiratory tract, with epithelial necrosis and loss of the upper respiratory tract and alveolar edema with fibrin, mixed alveolar inflammation, and hemorrhage in the lung. No NOAEL could be determined for Phytol based on the current study design. The LOAEL for inhalation administration is considered ≤ 109.0 / 10.9 mg/kg/day presented/deposited dose.

Exposure to PG concentrations of 4.427 mg/L and presented/deposited doses of up to 1151.7/115.2 mg/kg over 14 days resulted in sporadic clinical signs including pilorection, hyperactivity and rapid respiration. All animals recovered before the next exposure. No TA related changes in body weights gross pathology or clinical pathology parameters were detected. All microscopic findings were considered non-adverse. The NOAEL for PG inhalation in rats after 14 day exposure is considered 1151.7/115.2 mg/kg (presented/deposited dose).

LOVELACE BIOMEDICAL

Pathology Report

Study Title:	14-Day Inhalation Toxicology Study in Male and Female Sprague Dawley Rats
Lovelace Protocol Number:	FY19-149
Sponsor:	Canopy Growth USA LLC 1 Hershey Drive Smiths Falls, Ontario K7A 0A8
Test Facility:	Lovelace Biomedical 2425 Ridgecrest Drive SE Albuquerque, NM 87108 Courier Address and Location of Laboratory: Bldg 9217, Area Y Kirtland Air Force Base Albuquerque, NM 87115

Prepared by:

[redacted]

Date

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1 STUDY SUMMARY

The primary objective of this study is to evaluate and compare the potential toxicity of two vaporized test materials, phytol or propylene glycol (PG), when administered to Sprague Dawley rats via nose-only inhalation at 5 different dose levels (exposure duration controlled).

A total of 116 rats (58 males and 58 females) were used for study purposes. Fifty-five (55) of each sex were randomized to study groups (with 3 of each gender being designated as spares). Rats were randomized into 11 groups (5M/5F per group) and exposed to filtered air or a test article aerosol concentration of a nominal 5 mg/L via nose-only inhalation for daily durations of 0.5, 1, 2, 4, or 6 hours for up to 14 consecutive days. Scheduled necropsy was on the day following their last exposure (day 15).

At the scheduled sacrifice tissues were collected and fixed for histopathologic examination. Refer to Lovelace Biomedical protocol FY19-149 for details.

Early distress and deaths in 4 hour and 6 hour exposed Phytol groups led to euthanasia of all remaining Phytol animals in all groups on day 2. Gross lung discoloration in 4 and 6 hour Phytol exposure animals correlated with moderate to marked alveolar edema with fibrin, mild to marked mixed alveolar inflammation, and mild to marked hemorrhage within alveoli. In animals of lesser duration exposure groups, similar but dose-responsive and less severe changes were present, and the mixed inflammation demonstrated a distinct centriacinar (the junction of the conducting airways with the gas exchange area of the lung) distribution in these animals. However, lung changes in all Phytol groups were considered adverse.

All Propylene Glycol exposed animals survived until the designated euthanasia on day 15. Tissues were grossly unremarkable, and exposure related microscopic changes were limited to the larynx and lung. Minimal to mild alteration of laryngeal epithelium characterized by flattening and increased cell layers was present somewhat sporadically in an Air control and in some 4 and 6 hour PG exposed animals. In the lung, minimal increases in macrophages were seen in some 1, 4 and 6 hour exposed animals. Both laryngeal alteration and minor macrophage increases are common changes with inhalation exposure in rats and are considered non-adverse in this study.

2 INTRODUCTION

The Sponsor is testing several common chemical formulations for possible use in vaping or electronic-cigarettes. The current study is designed to test and compare the effects of two test articles (TAs) after 14-day repeated dose nose-only inhalation at different dose levels to Sprague Dawley rats. [redacted]

3 MATERIALS AND METHODS

3.1 Study Design

The experimental design is shown in **Error! Reference source not found.**~~Table 1~~.

Table 1. Experimental Design (adapted from protocol)

Group	Treatment	Target Aerosol Concentration (mg/L)	Exposure Duration (h)	Presented / Deposited Dose (mg/kg)*	Animals	
					Male	Female
1	Air Control	N/A	6	N/A	5	5
2	Phytol	5	0.5	129.5 / 12.9	5	5
3	Phytol		1	257.9 / 25.8	5	5
4	Phytol		2	517.9 / 51.8	5	5
5	Phytol		4	1033.2 / 103.3	5	5
6	Phytol		6	1549.8 / 155.0	5	5
7	PG	5	0.5	95.6 / 9.6	5	5
8	PG		1	191.2 / 19.1	5	5
9	PG		2	382.5 / 38.3	5	5
10	PG		4	765.3 / 76.5	5	5
11	PG		6	1151.7 / 115.2	5	5

* Phytol dose shown is for Day 1 of exposure; PG dose is the average daily dose.

3.2 Anatomic Pathology

3.2.1 Euthanasia Information

At scheduled necropsy or in cases of morbidity, animals were euthanized by intraperitoneal injection of an overdose of a barbiturate-based sedative.

3.2.2 Gross Observations

Briefly, per study protocol tissues were collected, examined, weighed, and representative samples preserved for histopathology. Weights were collected on [redacted] lungs, [redacted]

Tissues designated for histopathology (nose/turbinates, larynx, trachea, lung, liver, kidney) were fixed in 10% neutral buffered formalin (NBF). Lung lobes were instilled [redacted] with NBF at 25cm hydrostatic pressure, [redacted]

3.2.3 Microscopic Observations

Tissues were trimmed and processed routinely, paraffin embedded, sectioned at 4 um, and stained with hematoxylin and eosin for microscopic examination.

Findings for a given tissue were graded subjectively and semi-quantitatively by a single pathologist on a scale of 1-5 (1 = Minimal, 2 = Mild, 3 = Moderate, 4 = Marked, 5 = Severe). [redacted] computer software/database was used for necropsy and histopathology data acquisition, reporting and analysis.

3.3 Compliance Statement

[redacted]

4 RESULTS & DISCUSSION

4.1 Survival

On study days 1 and 2, Phytol exposed groups 5 (4 h exposure) and 6 (6 h exposure) experienced numerous early deaths. These are designated with the Provantis removal reasons Found Dead (FD) or Moribund Euthanasia (ME) in Group 5 (6 FD, 1 ME) and Group 6 (6 FD, 1 ME). Due to severe clinical signs including respiratory distress and large number of early deaths, all remaining Phytol exposed animals (Groups 2-6) were euthanized on study day 2 with the [redacted] designation "Moribund Euthanasia (Phytol Groups- Early Study End)".

All Air control (Group 1) and Propylene Glycol (Groups 7-11) animals survived until designated sacrifice on day 15. See appendices for specific study day and removal reason for individual animals).

4.2 Gross Observations

Early deaths in Phytol groups 5 and 6 all demonstrated severely discolored purple lungs on gross examination. Many of the remaining phytol exposed animals of groups 2-6 demonstrated variable degrees of dark red discoloration varying from patchy to small multiple, punctate areas. Discolored areas generally correlated with histologic edema, hemorrhage and/or inflammation. Air Control and Propylene Glycol groups were grossly unremarkable. See appendices for detailed listing of gross observations and specific animal information.

4.3 Organ Weights

Organ weights were collected and reviewed as absolute organ weight, organ to body weight ratio, and organ to brain weight ratio versus Group 1 Air controls.

A dose responsive increase was present in available lung weights and lung to body weight ratio for all Phytol groups, with Group 6 lung weight increased over 4 fold that of Air controls.

Lung weights of Propylene Glycol exposed animals were unremarkable versus Air controls.

4.4 Microscopic Observations

There were treatment related observations in the tissues examined. A summary table of selected observations is presented below (Error! Reference source not found.~~Table 2~~). Refer to the appendices of this report for a complete matrix of all observations in all tissues.

4.4.1 Changes Related to Test Article Administration

Phytol exposed groups demonstrated prominent changes within the respiratory tract after 1 (Groups 5, 6) or 2 (Groups 2-4) days of exposure. Prominent changes in early deaths (especially in Groups 5 and 6) included dose-responsive degeneration and necrosis of epithelium within the nose/turbinates (multiple levels), larynx, and trachea. In the lungs of these animals the primary changes included pulmonary edema with fibrin, and widespread mixed cell inflammation with abundant macrophages, lymphocytes and neutrophils. Additional findings including hemorrhage and epithelial degeneration were also present in severely affected lungs.

For animals in Phytol groups 2, 3 and 4 which survived to the early euthanasia [redacted] designation "Moribund Euthanasia (Phytol Groups- Early Study End)"], there were less severe changes, although the mixed cell inflammation in the lungs was present in all animals and demonstrated a distinct centriacinar distribution. The findings in the nose, airways and lungs of all Phytol groups are considered adverse.

A summary table with selected findings and tissues representative of the changes important in the interpretation of this study is included below (Table 2; level 3 of the nose/turbinates is representative of the nasal changes and is shown). See appendices for detailed listing of microscopic observations and specific animal information.

Table 2. Selected Microscopic Observations Summary – Phytol Exposure

Gender		Males						Females					
Group Description		Air	Phytol	Phytol	Phytol	Phytol	Phytol	Air	Phytol	Phytol	Phytol	Phytol	Phytol
Exposure Duration		6 hr	0.5 hr	1 hr	2 hr	4 hr	6 hr	6 hr	0.5 hr	1 hr	2 hr	4 hr	6 hr
[redacted] Group Number]		1	2	3	4	5	6	1	2	3	4	5	6
Number of Animals		5	5	5	5	5	5	5	5	5	5	5	5
NOSE/TURBINATE 3 (Number examined)		5	5	5	5	5	5	5	5	5	5	5	5
Necrosis, Olfactory Epithelium	**Incidence**	**0**	**4**	**5**	**5**	**5**	**5**	**0**	**1**	**5**	**5**	**5**	**5**
	Minimal - 1	-	2	2	-	-	-	-	1	1	-	-	-
	Mild - 2	-	2	1	-	-	-	-	-	2	-	2	-
	Moderate - 3	-	-	2	3	2	1	-	-	2	2	3	2
	Marked - 4	-	-	-	2	3	4	-	-	-	3	-	3
LARYNX (Number examined)		5	5	5	5	5	5	5	5	5	5	5	5
Degeneration, Necrosis with Sloughing (Epithelium)	**Incidence**	**0**	**0**	**0**	**1**	**5**	**0**	**0**	**0**	**0**	**0**	**2**	**1**
	Minimal - 1	-	-	-	-	1	-	-	-	-	-	1	1
	Mild – 2	-	-	-	1	1	-	-	-	-	-	-	-
	Moderate - 3	-	-	-	-	2	-	-	-	-	-	1	-
	Marked – 4	-	-	-	-	1	-	-	-	-	-	-	-
LUNGS (Number examined)		5	5	5	5	5	5	5	5	5	5	5	5
Edema with Fibrin (Alveolar)	**Incidence**	**0**	**0**	**0**	**2**	**5**	**5**	**0**	**0**	**0**	**0**	**5**	**5**
	Minimal - 1	-	-	-	2	-	-	-	-	-	-	-	-
	Mild - 2	-	-	-	-	-	-	-	-	-	-	1	1
	Moderate - 3	-	-	-	-	-	1	-	-	-	-	2	1
	Marked +- 4	-	-	-	-	5	4	-	-	-	-	2	3
Inflammation, Mixed Cell (Alveolar)	**Incidence**	**0**	**0**	**0**	**0**	**4**	**5**	**0**	**0**	**1**	**4**	**5**	**5**
	Minimal - 1	-	-	-	-	-	-	-	-	-	3	-	-
	Mild - 2	-	-	-	-	-	-	-	-	-	-	1	-
	Moderate - 3	-	-	-	-	1	3	-	-	1	1	2	3
	Marked - 4	-	-	-	-	3	2	-	-	-	-	2	2
Increase, Macrophages	**Incidence**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Minimal - 1	1	-	-	-	-	-	-	-	-	-	-	-

In contrast to the changes seen with Phytol, animals exposed to Propylene Glycol were largely unremarkable, with only minor and inconsistent changes. In the larynx, minimal epithelial alteration characterized by flattening and slight increase in cell layers was occasionally present, and minimal increases in unremarkable alveolar macrophages were present in some animals. Both changes are well recognized, common findings in inhalation exposures. Both changes were sporadic, but slightly more frequent in animals in higher exposure duration groups. At the minimal to mild levels seen in this study, neither change is considered to be adverse.

A summary table with selected findings and tissues representative of the changes important in the interpretation of this study is included below (Table 3). For ease of comparison, 2 of the primary lung findings in Phytol exposed animals (edema and inflammation) are included in the summary table even though they were not present in Propylene Glycol exposed animals. See appendices for detailed listing of microscopic observations and specific animal information.

Table 3. Selected Microscopic Observations Summary – Propylene Glycol Exposure

Gender		Males						Females					
Group Description		**Air**	**PG**	**PG**	**PG**	**PG**	**PG**	**Air**	**PG**	**PG**	**PG**	**PG**	**PG**
Exposure Duration		6 hr	0.5 hr	1 hr	2 hr	4 hr	6 hr	6 hr	0.5 hr	1 hr	2 hr	4 hr	6 hr
[redacted] Group Number]		**1**	**7**	**8**	**9**	**10**	**11**	**1**	**7**	**8**	**9**	**10**	**11**
Number of Animals		5	5	5	5	5	5	5	5	5	5	5	5
LARYNX (Number examined)		5	5	5	5	5	5	5	5	5	5	5	5
Alteration (Epithelium)	**Incidence**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Minimal - 1	-	-	-	-	-	-	-	-	-	-	-	-
LUNGS (Number examined)		5	5	5	5	5	5	5	5	5	5	5	5
Edema with Fibrin (Alveolar)	**Incidence**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Minimal - 1	-	-	-	-	-	-	-	-	-	-	-	-
Inflammation, Mixed Cell (Alveolar)	**Incidence**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Minimal - 1	-	-	-	-	-	-	-	-	-	-	-	-
Increase, Macrophages	**Incidence**	**1**	**0**	**1**	**0**	**1**	**3**	**0**	**0**	**2**	**0**	**0**	**1**
	Minimal - 1	1	-	1	-	1	3	-	-	2	-	-	1

4.4.2 Changes Unrelated to Test Article

Minor, sporadic incidental or "background" histologic findings, as expected, occurred in this study (*e.g.* minor mononuclear cell infiltrates). Such incidental findings could not be differentiated in character or severity from Air controls, and/or were widely scattered and were not related to test article.

5 CONCLUSIONS

Inhalation exposure of Sprague-Dawley rats to Phytol for 1 or 2 days resulted in prominent adverse changes in the respiratory tract under the conditions of this study. In 4 and 6 hour Phytol exposure animals, (all found dead or euthanized moribund), epithelial necrosis and loss was present in the upper respiratory tract (nose, larynx, trachea), and the lungs demonstrated moderate to marked alveolar edema with fibrin, mild to marked mixed alveolar inflammation, and mild to marked hemorrhage within alveoli. Similar changes were present in 0.5, 1 and 2 hour Phytol exposed

animals, but they were dose-responsive and less severe in animals in lesser duration exposure groups, and the mixed inflammation demonstrated a distinct centriacinar (the junction of the conducting airways with the gas exchange area of the lung) distribution in these animals. However, lung changes in all Phytol groups were considered adverse.

Inhalation to propylene glycol for 14 days resulted in only minimal to mild alteration in the laryngeal epithelium (base of the larynx) and minimal macrophage increases within the lung in some animals. Neither of these minor changes was considered adverse at any dose level examined in this study.

Appendix I

Intergroup Comparison of Gross Observations

Pathology - Intergroup Comparison of Pathology Observations

For Study:	19-149 - 14-Day Inhalation Toxicology Study in Male and Female Sprague Dawley Rats
Job Number/Requested By:	141834, [redacted]
Animal Reference:	Animal Name
Animals Excluded:	None
Day Numbers:	All
Groups:	All
Observation Type:	Gross
Observation Summary:	Incidence
Report Format:	Group within Sex
Tissues:	All
Rationalization Set:	None
Removal Reasons:	All
Completed Animals Only:	No
Animals with Observations Only:	No
Tissues with Observations Only:	No
Split Observations by:	SEVERITY
Split Table by:	Sex
Use Alternative Descriptions:	No
Repeat First Group on Each Page:	No
Style:	Landscape - 12 Columns
Include:	NVL Tissues; NE Tissues; Locators; COLOR - CONSISTENCY; SYMMETRY - SHAPE; DISTRIBUTION - QUANT

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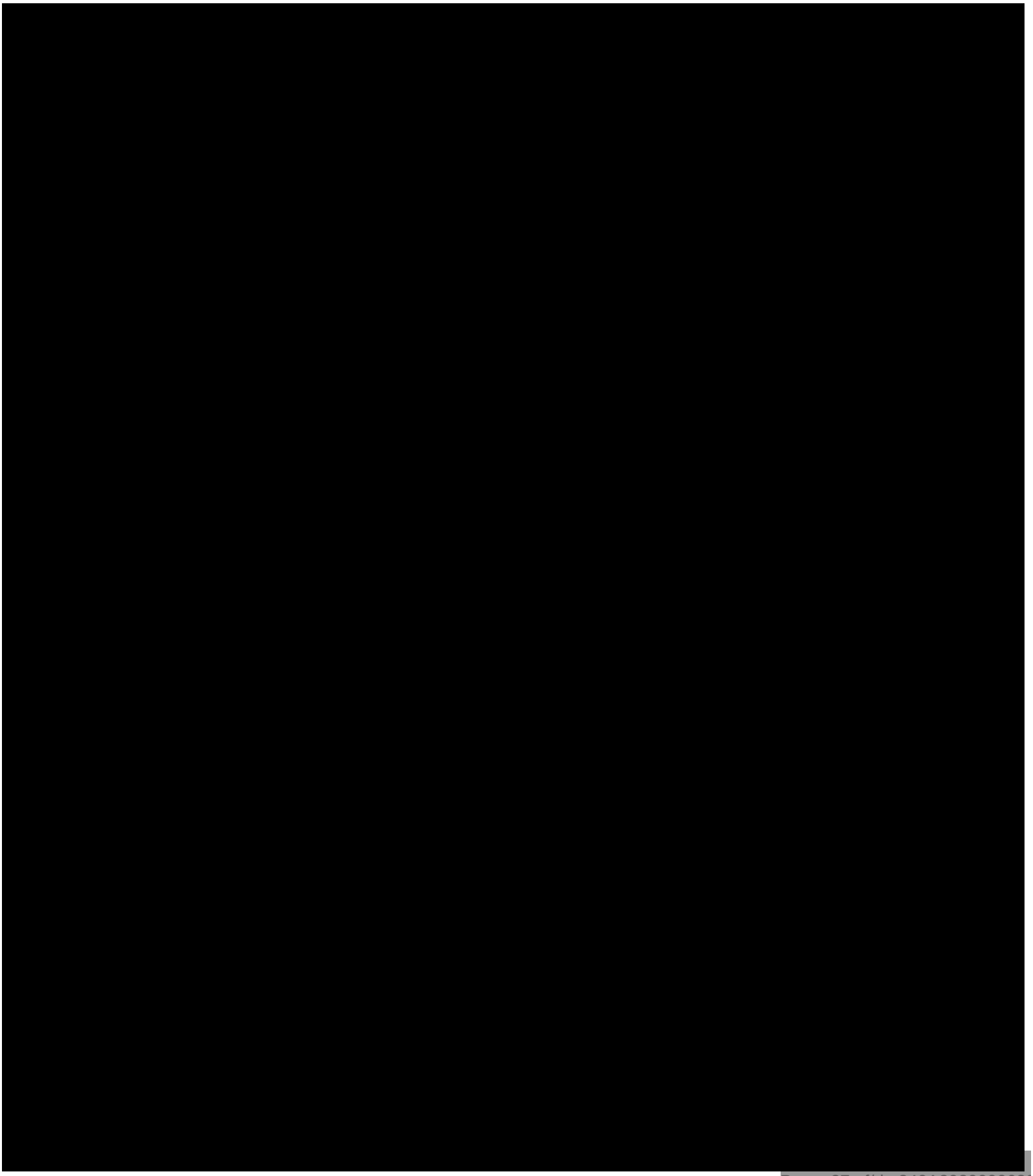

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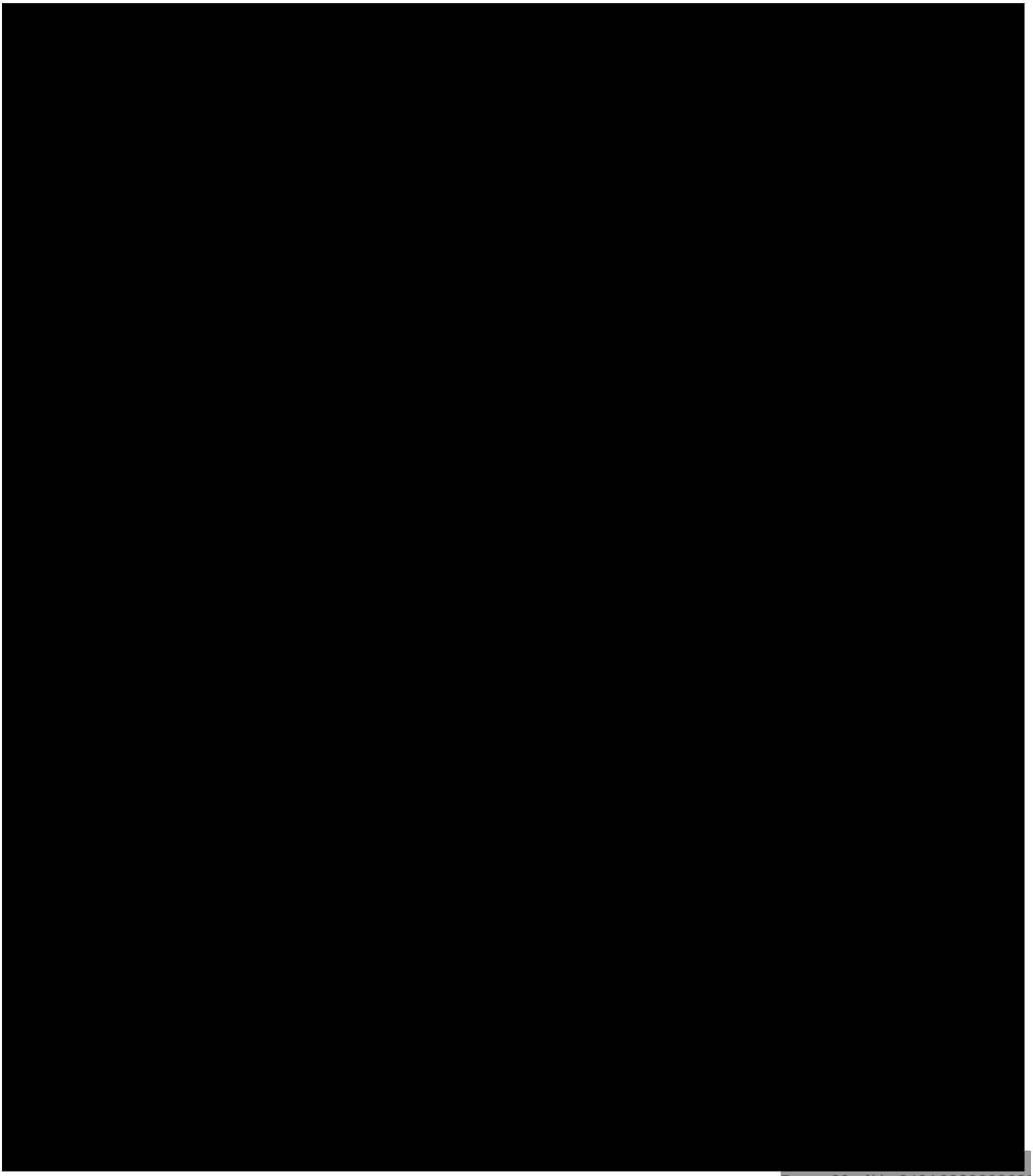

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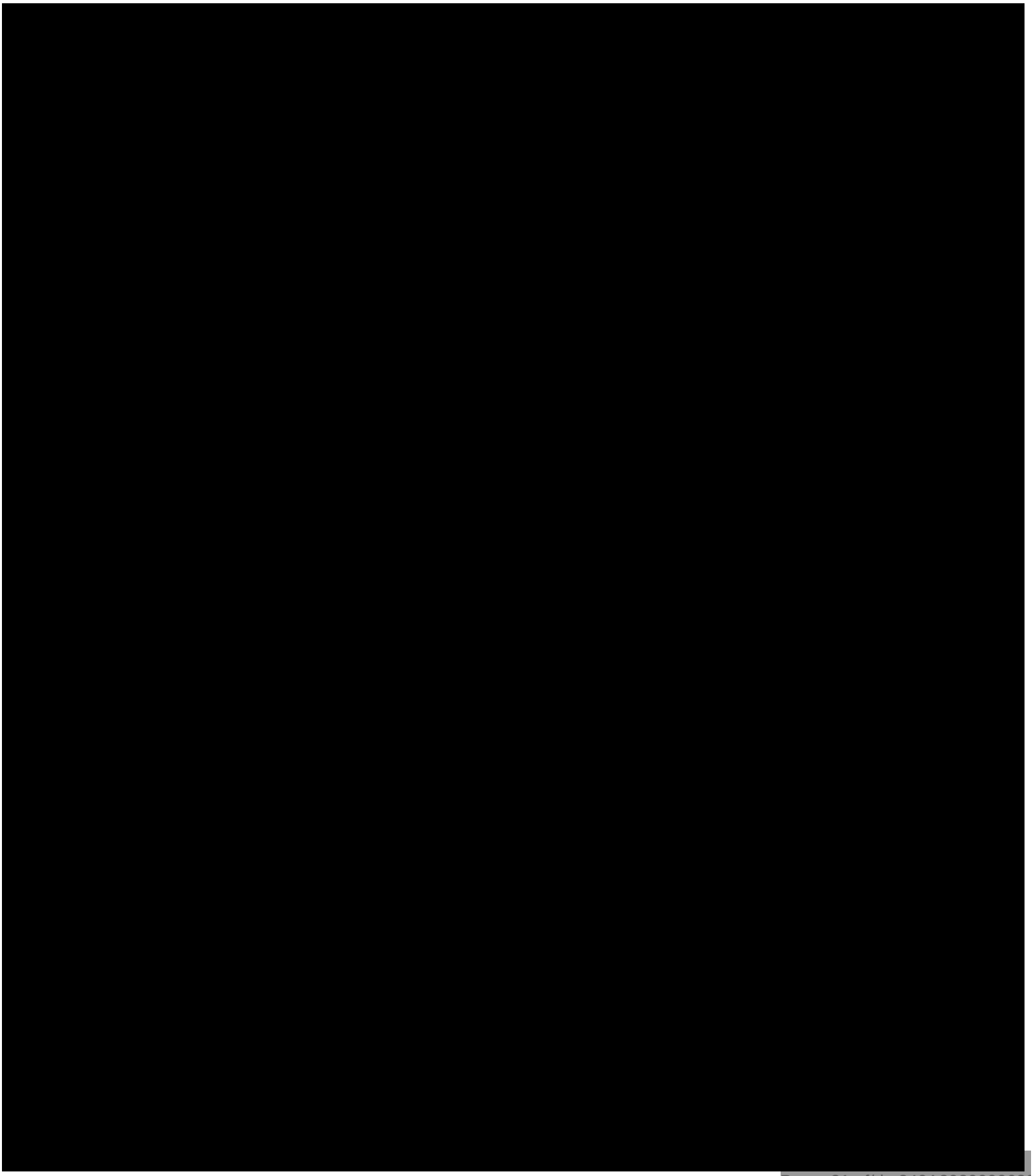

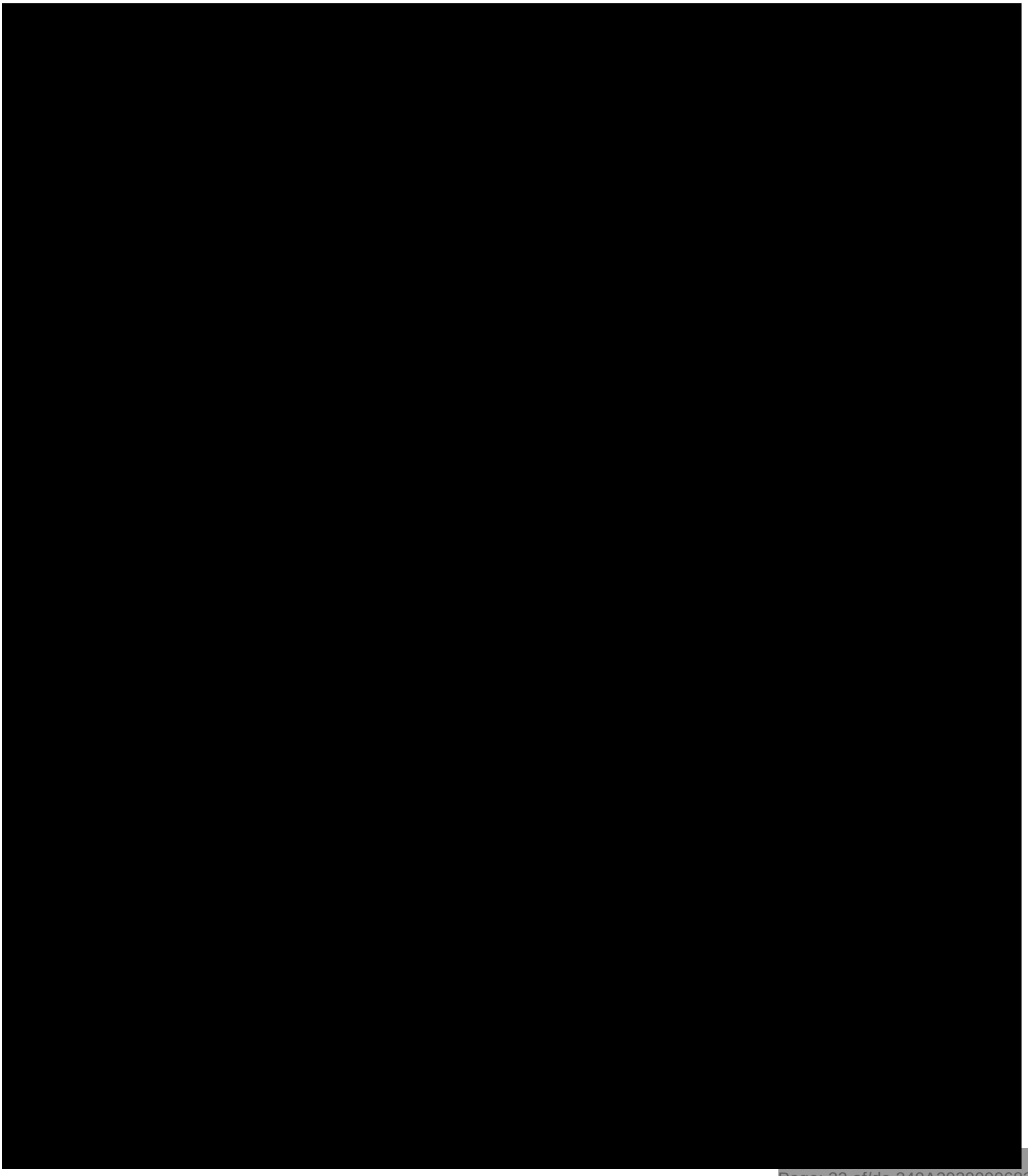

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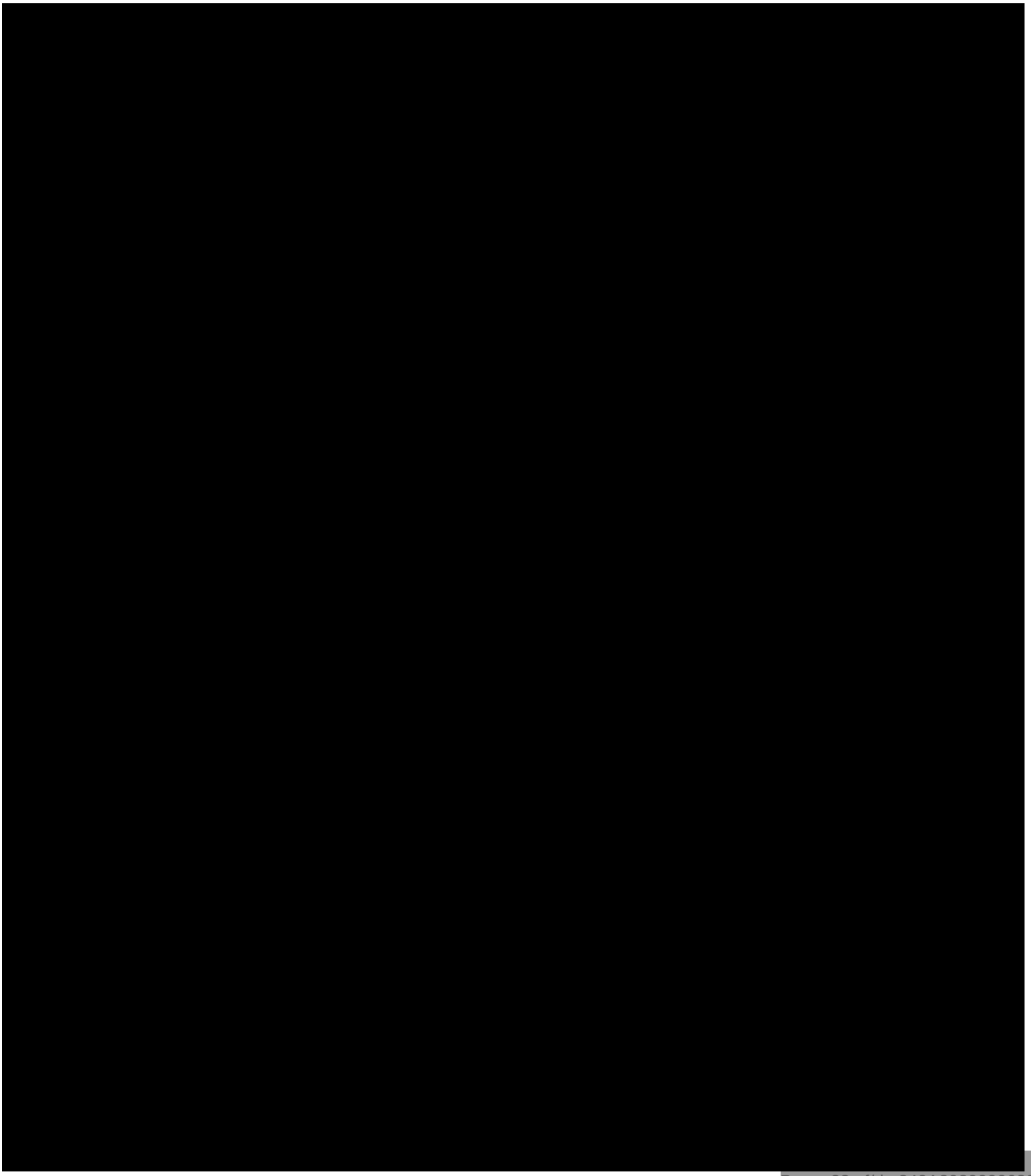

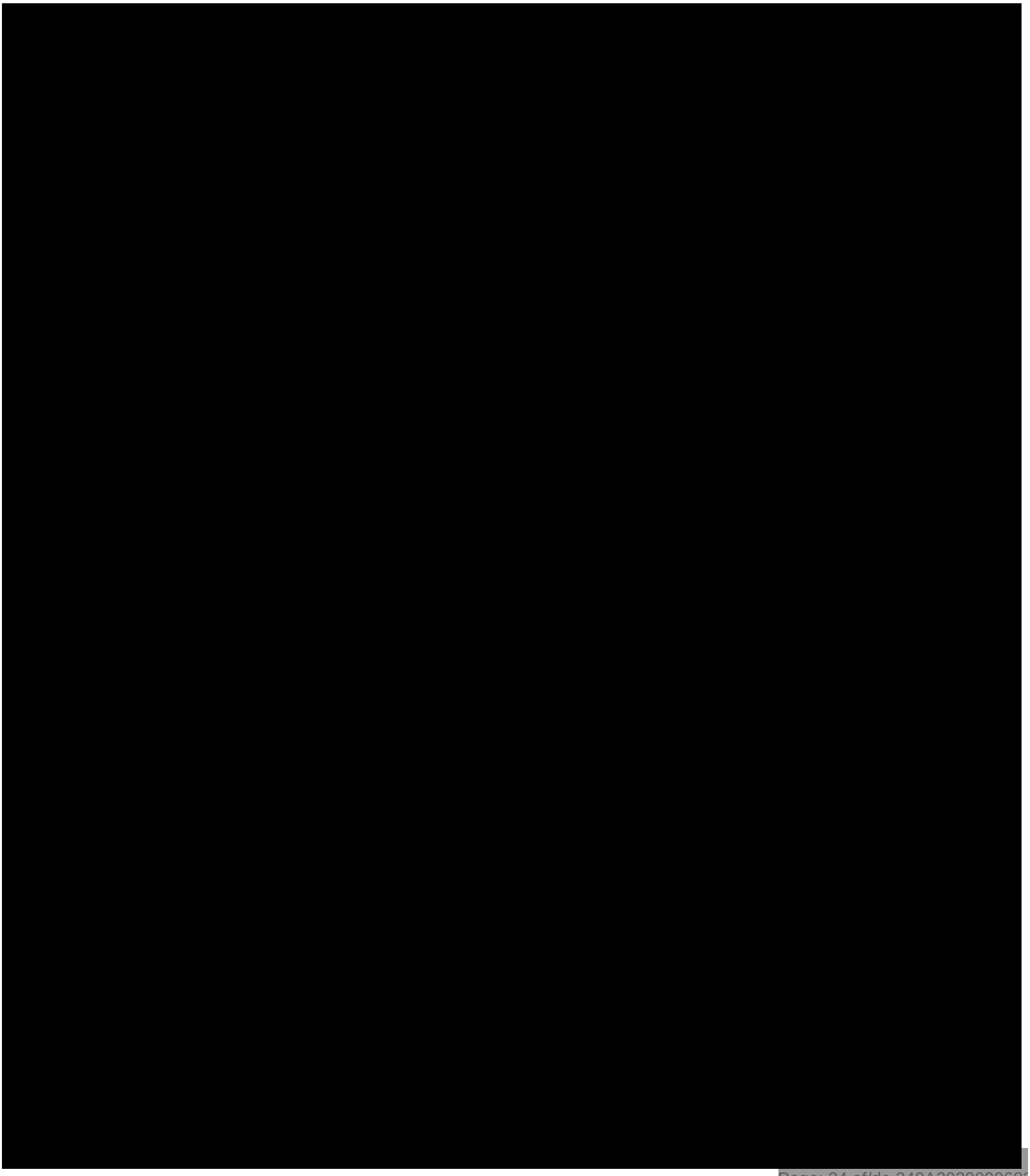

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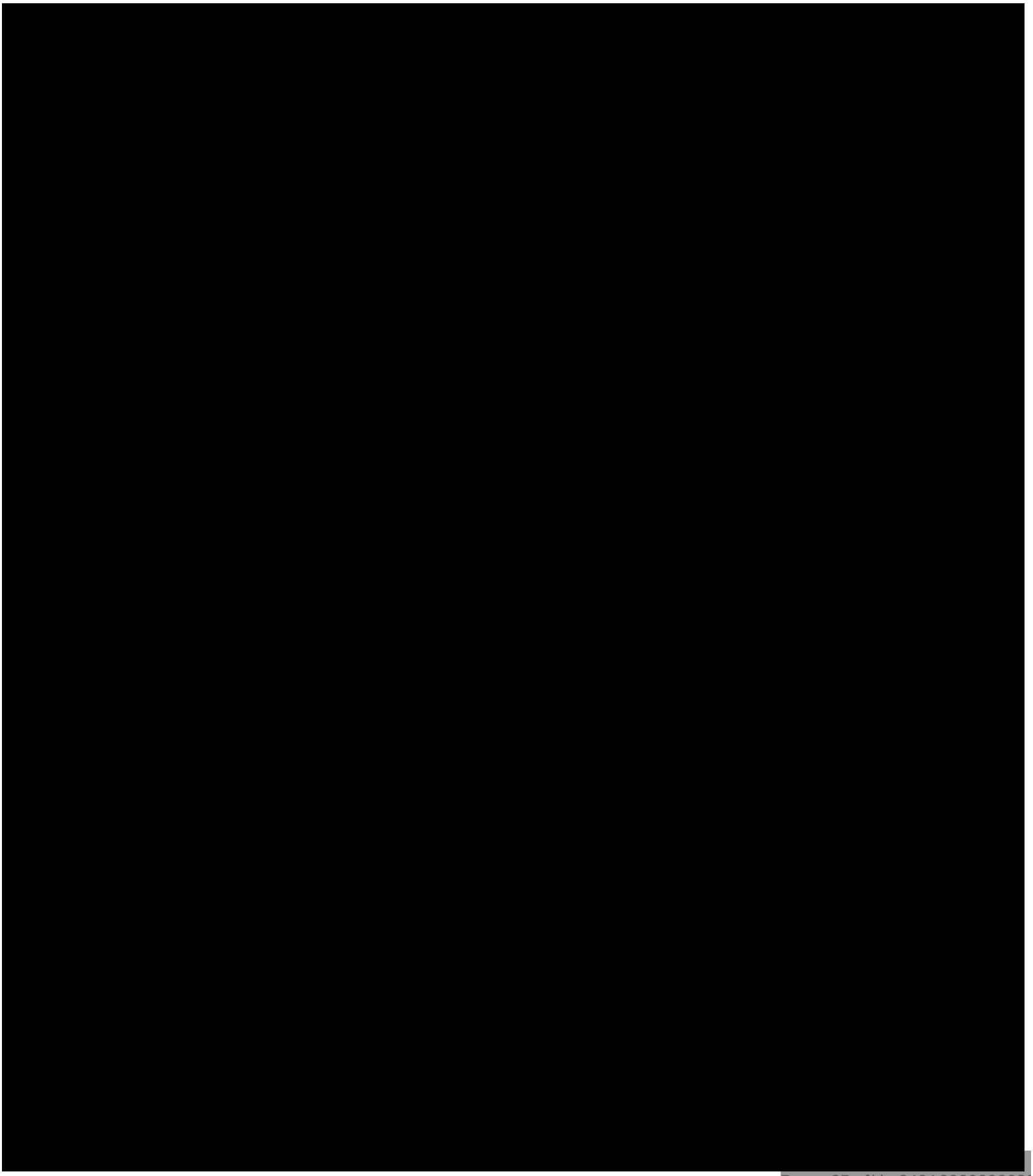

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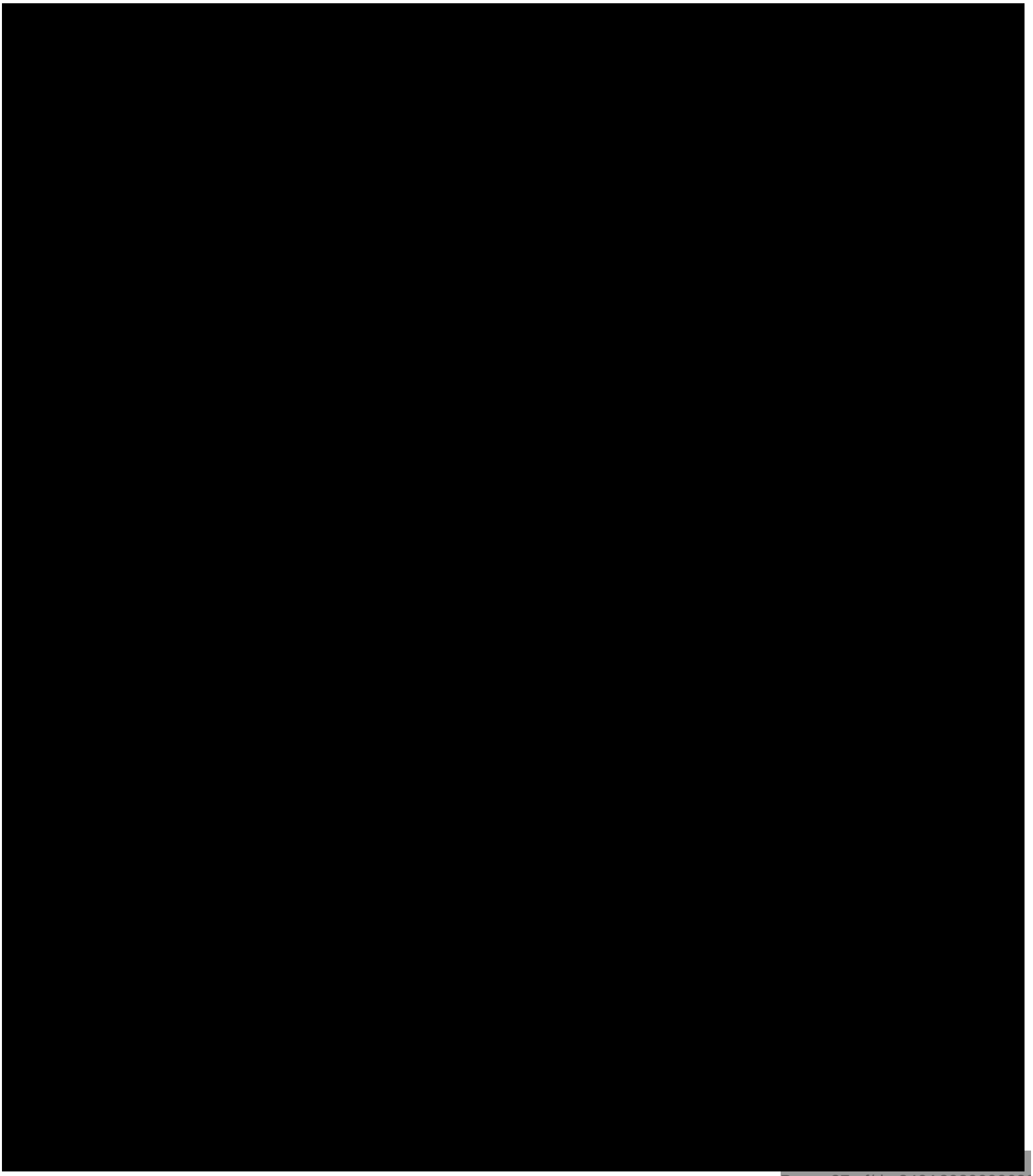

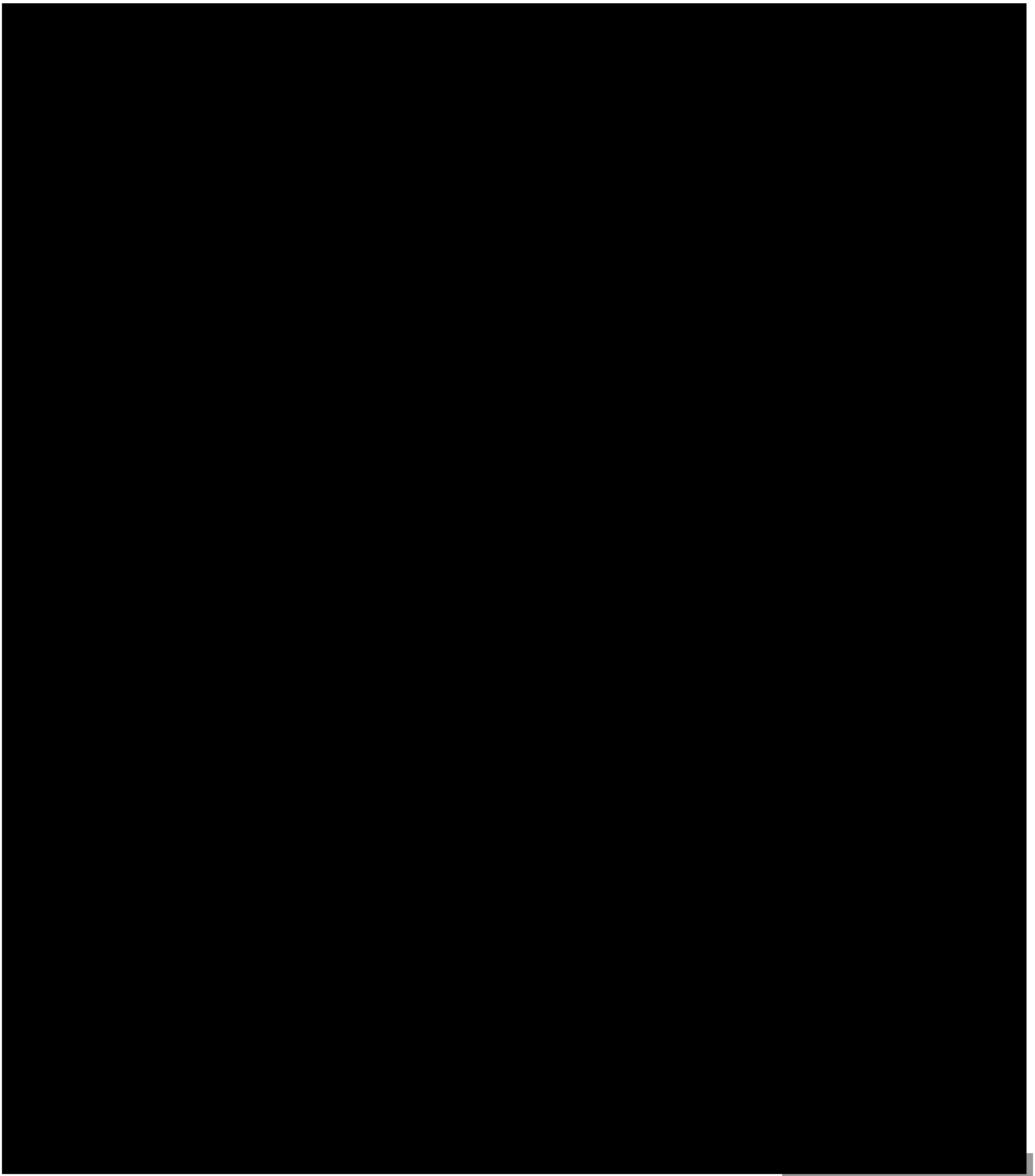

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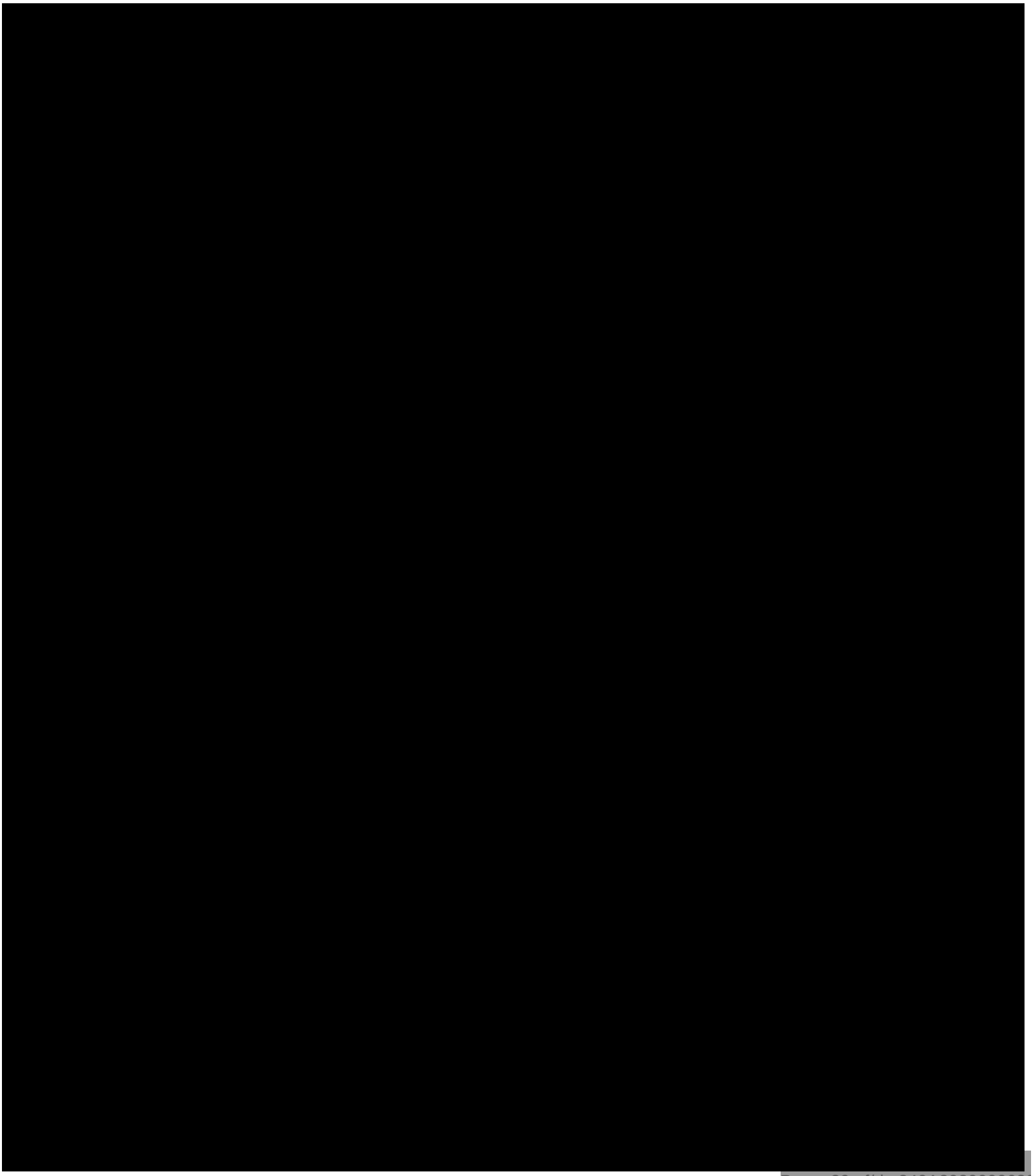
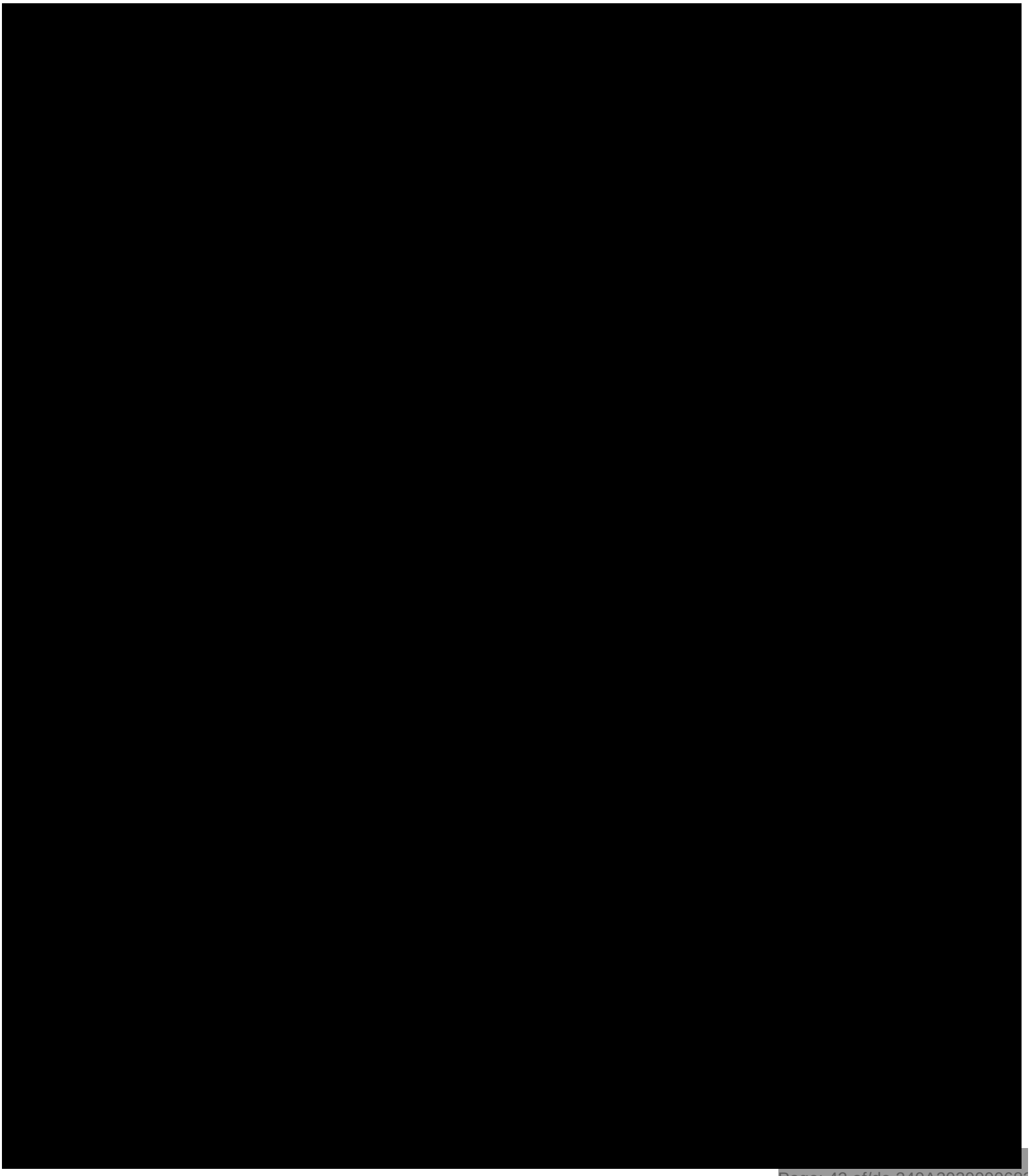


Appendix II

Intergroup Comparison of Histopathology Observations

Pathology - Intergroup Comparison of Pathology Observations

For Study:	19-149 - 14-Day Inhalation Toxicology Study in Male and Female Sprague Dawley Rats
Job Number/Requested By:	141848, [redacted]
Animal Reference:	Animal Name
Animals Excluded:	None
Day Numbers:	All
Groups:	All
Observation Type:	Histo - Neoplastic and Non-Neoplastic
Observation Summary:	Incidence
Report Format:	Group within Sex
Tissues:	All
Rationalization Set:	None
Removal Reasons:	All
Completed Animals Only:	No
Animals with Observations Only:	No
Tissues with Observations Only:	No
MPF Only:	No
Extended Findings:	None
Split Observations by:	GRADE
Split Table by:	Sex
Use Alternative Descriptions:	No
Repeat First Group on Each Page:	No
Style:	Landscape - 12 Columns
Include:	NVL Tissues; NE Tissues; Locators; Neoplastic - QUALIFIERS; TUMOUR TYPE; ORIGIN; CLASSIFICATION; Non-neoplastic - QUALIFIERS; SYMMETRY_SIZE; DISTRIBUTION



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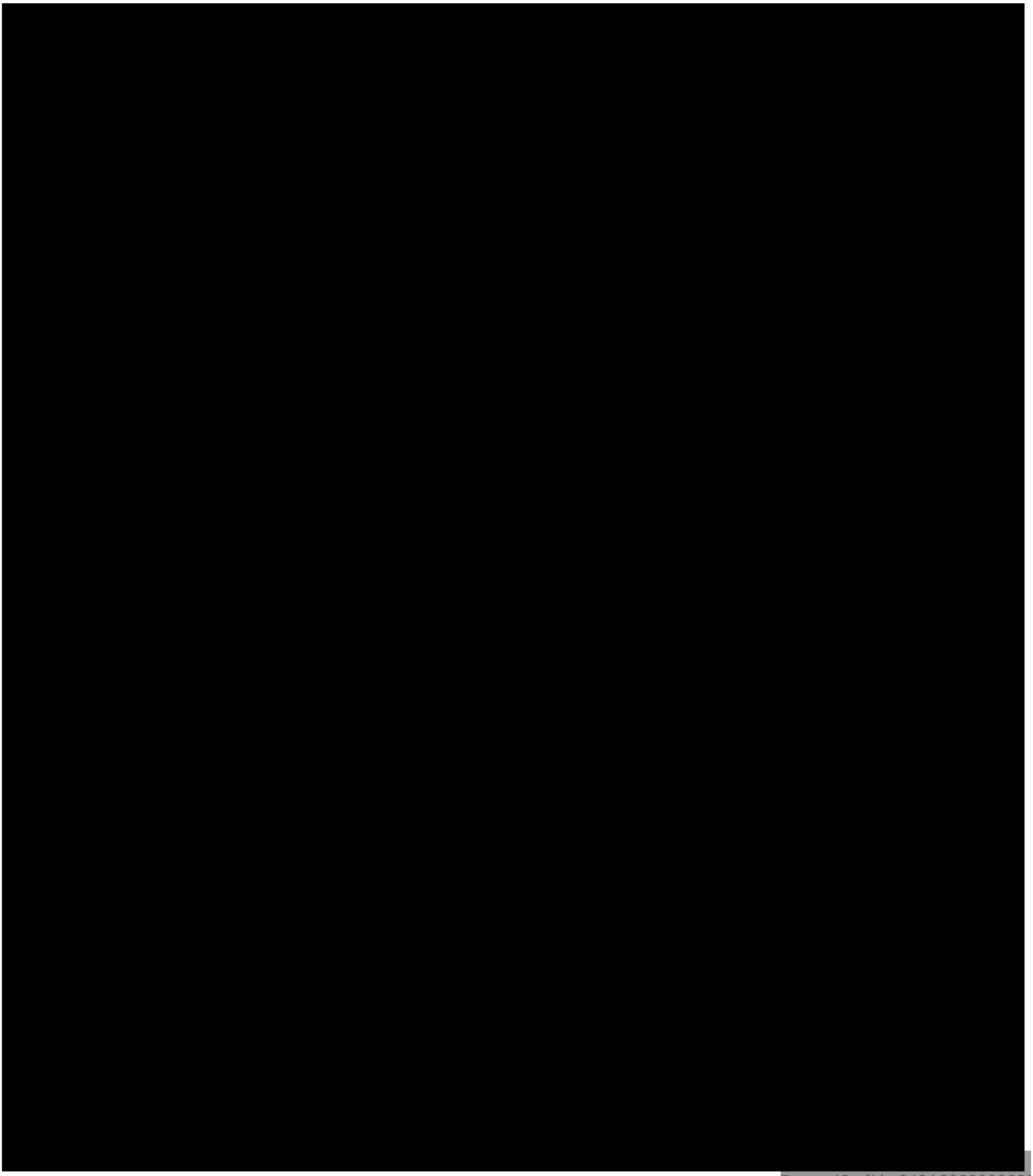

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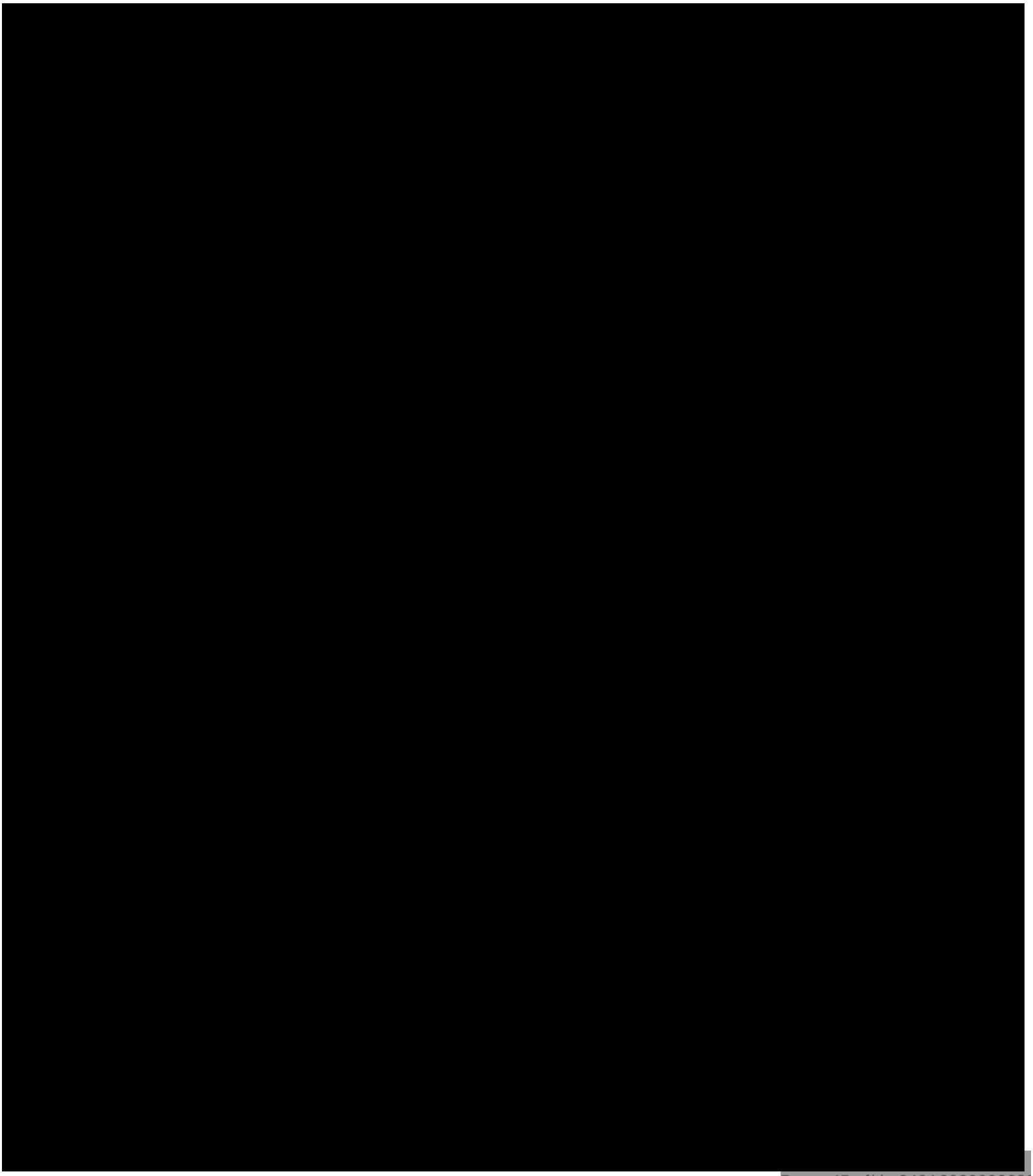

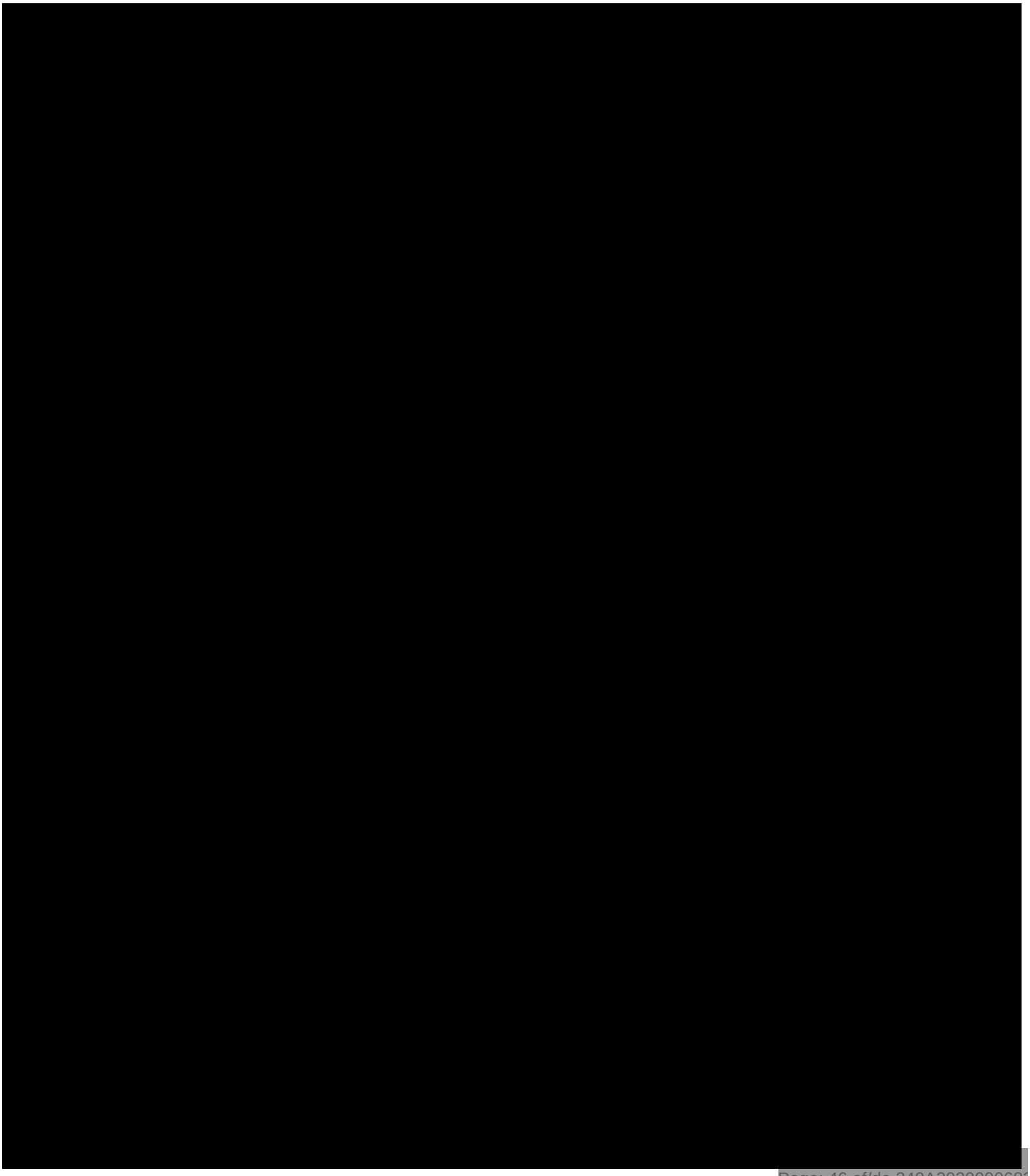

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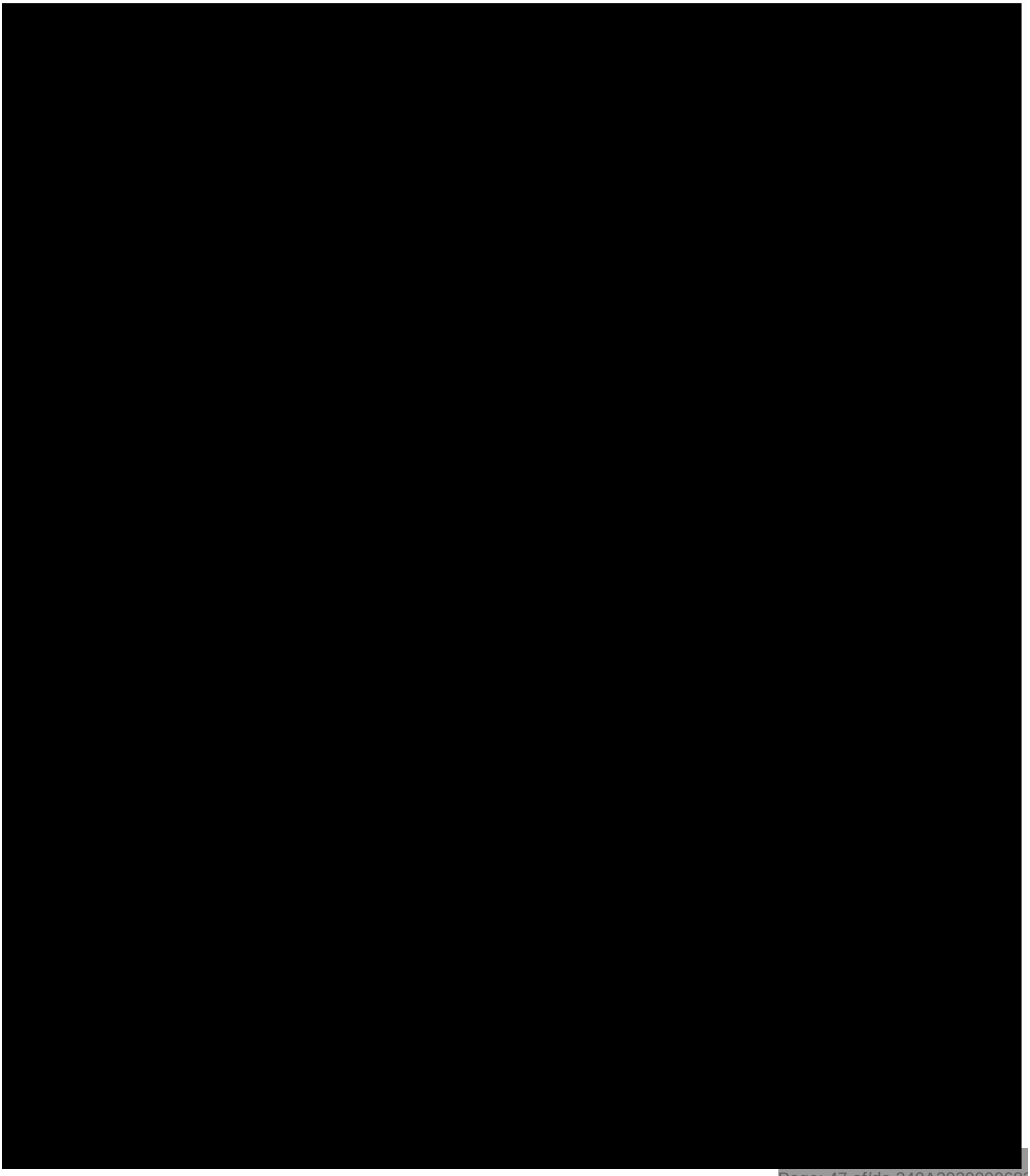

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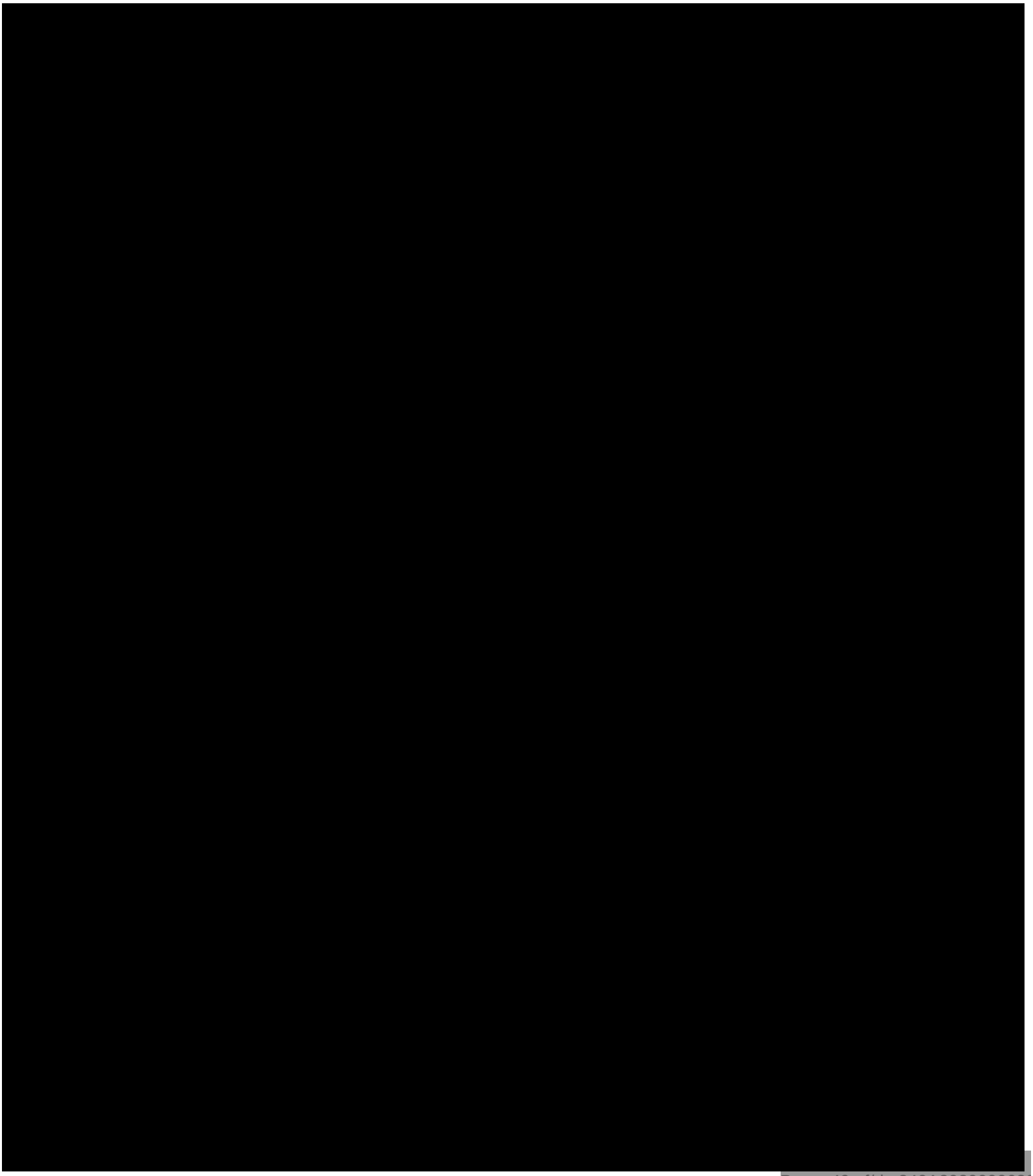

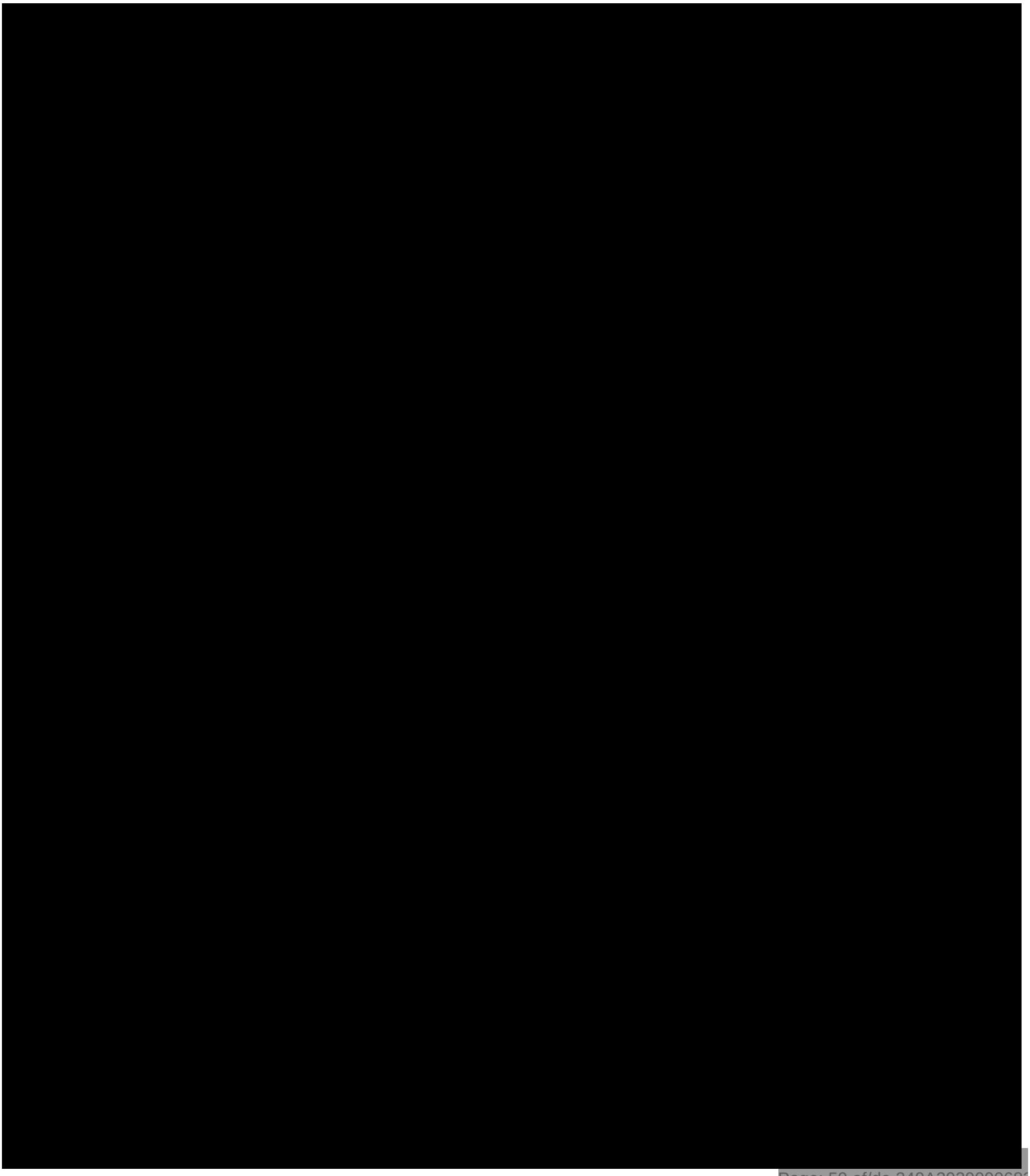

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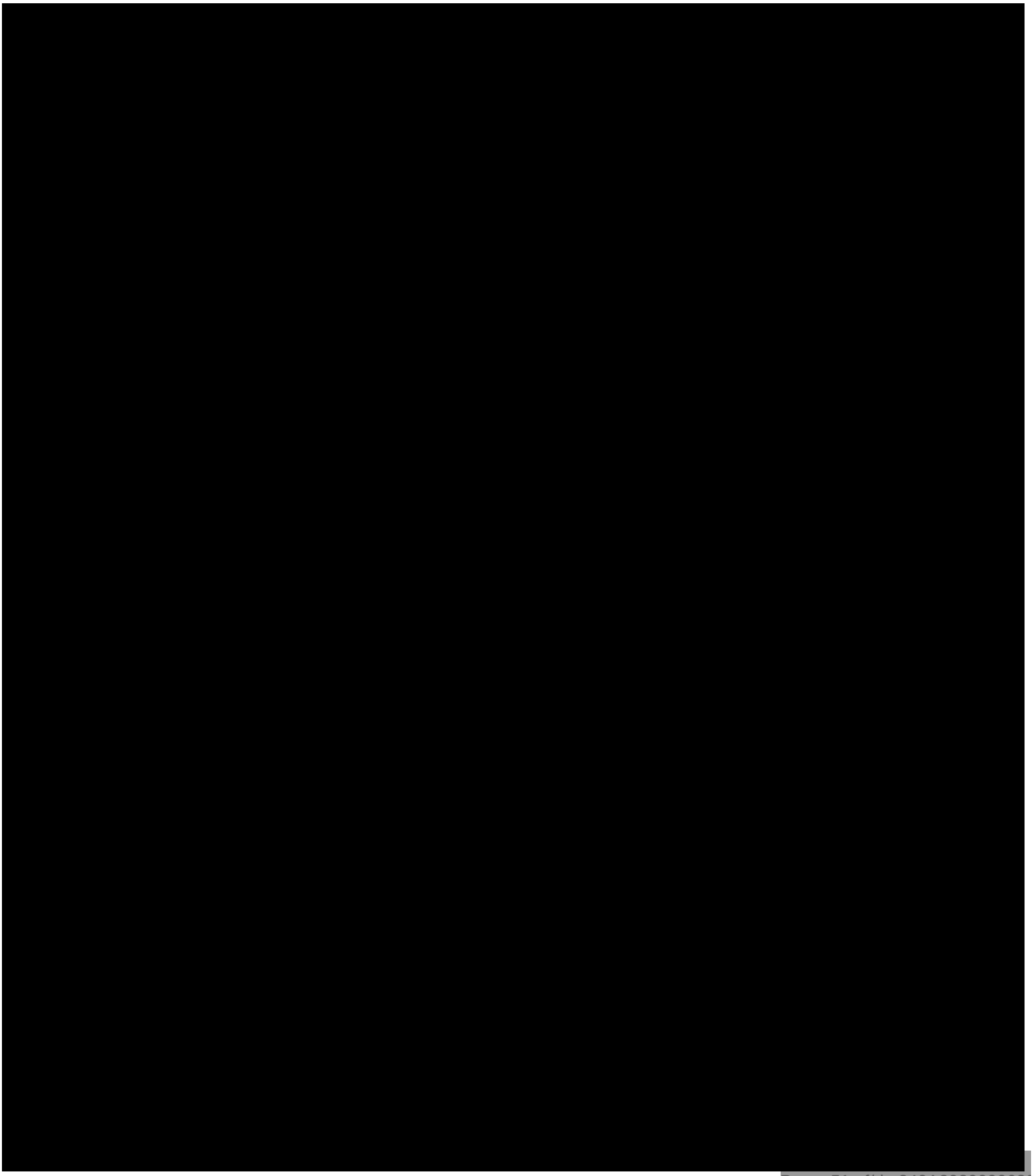

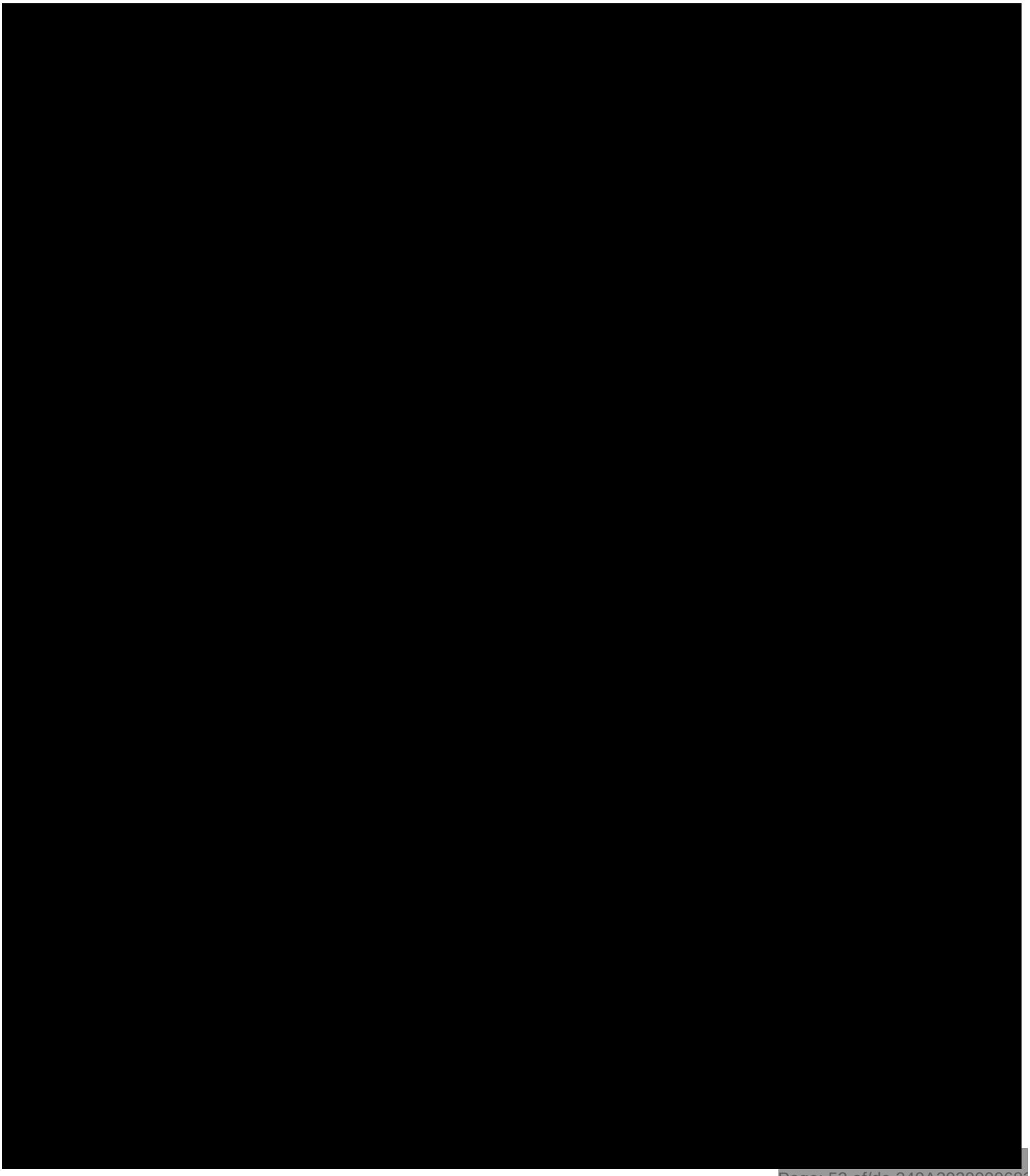

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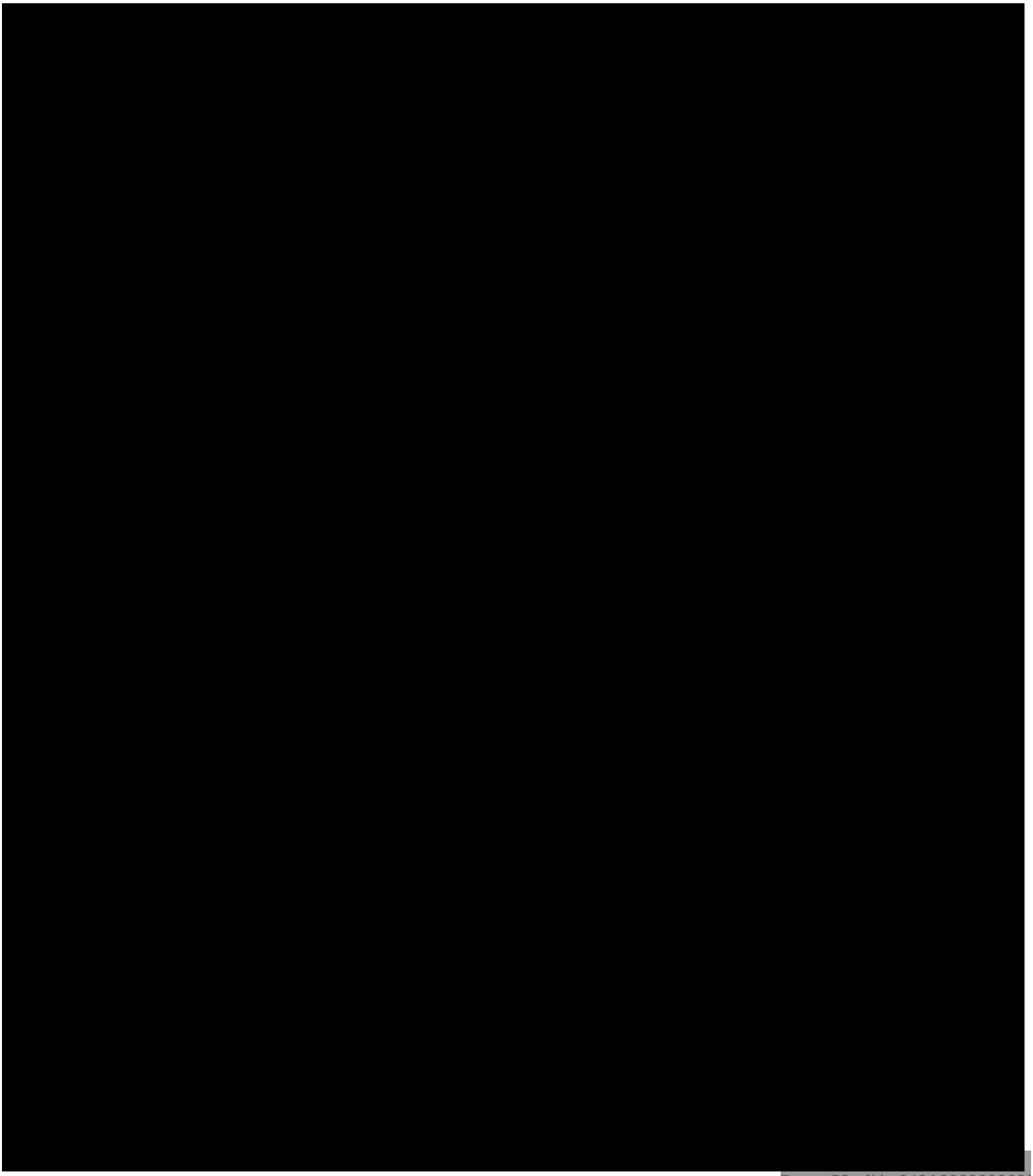

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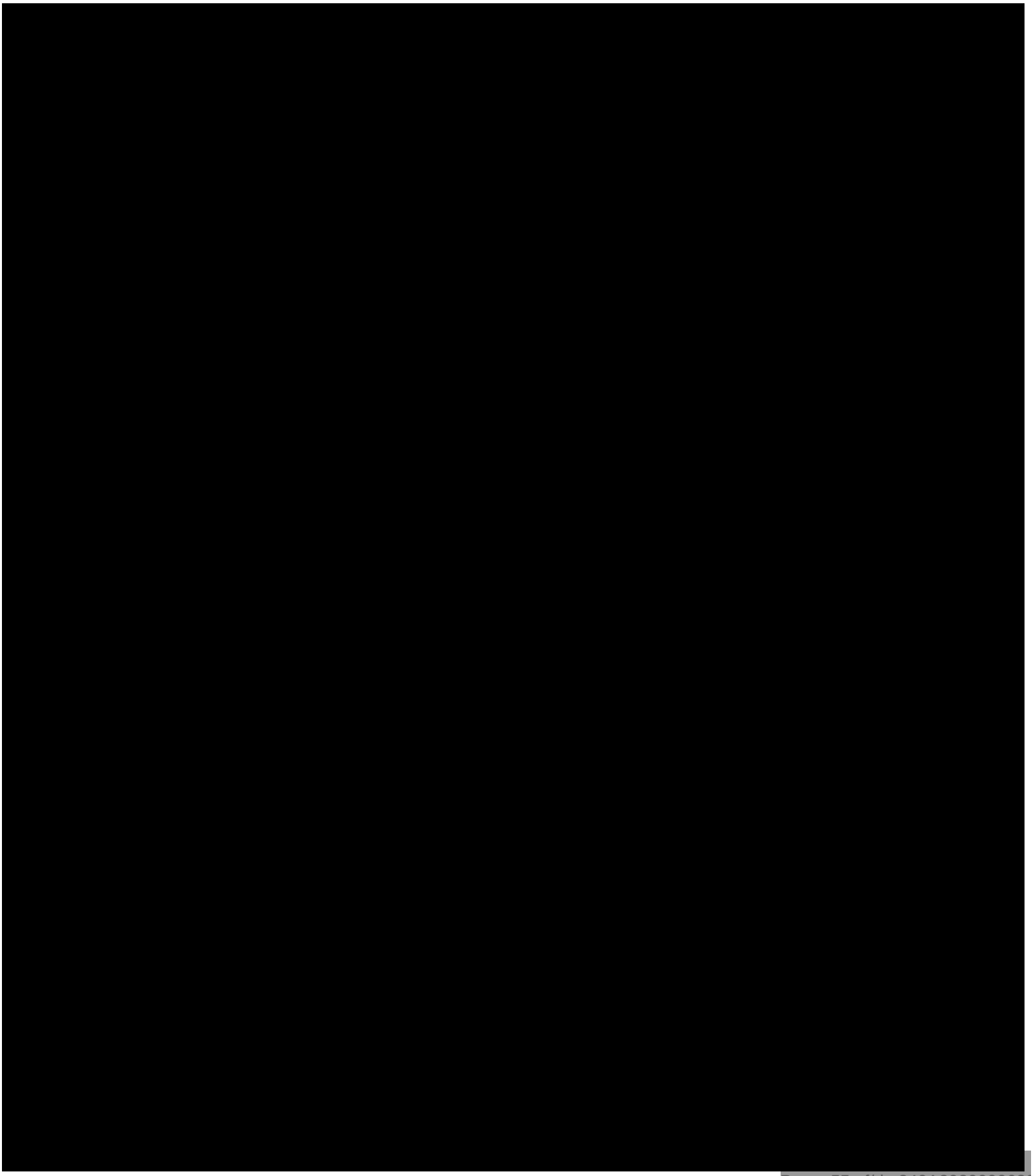

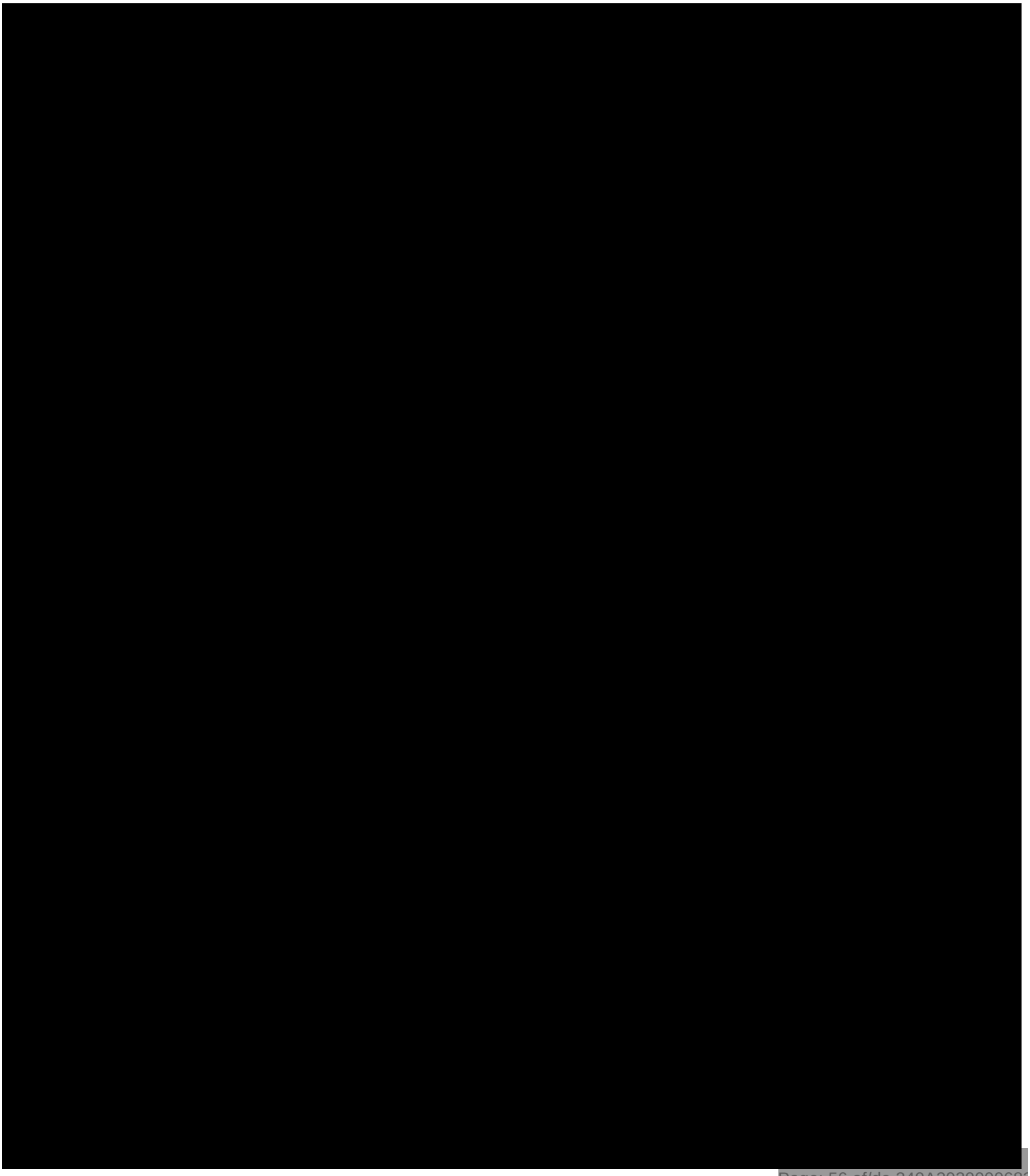

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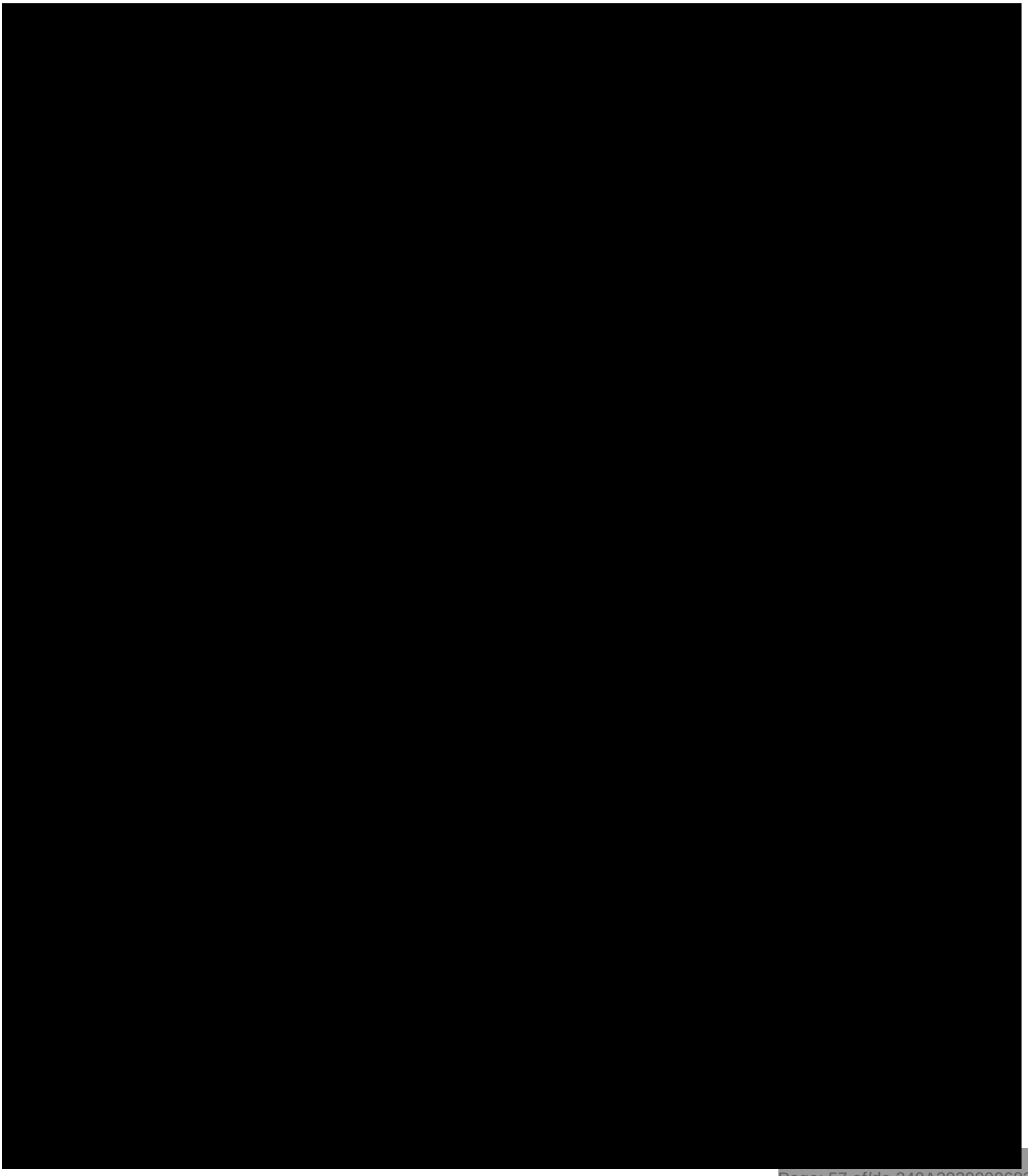

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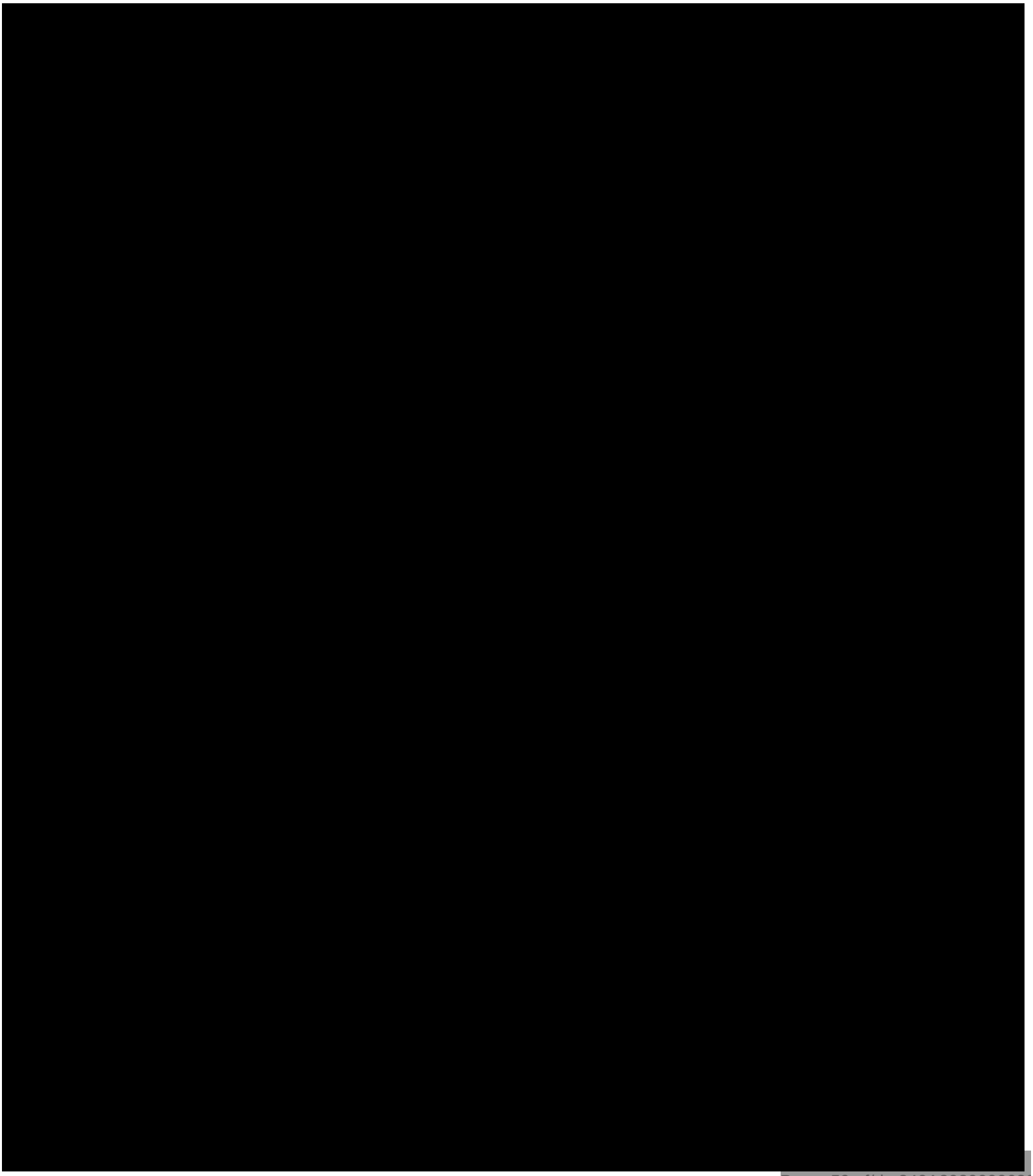

Appendix III

Individual Animal Data

Pathology - Individual Animal Data

For Study:	19-149 - 14-Day Inhalation Toxicology Study in Male and Female Sprague Dawley Rats
Job Number/Requested By:	141841/[redacted]
Animal Reference:	Animal Name
Animals Included:	All
Page Break on Animal:	Yes
Day Numbers:	All
Groups:	All
Observation Type:	Gross and Histo
Tissues:	All
Removal Reasons:	All
Use Alternative Descriptions:	No
Style:	Landscape - Condensed
Gross Pathology Observations:	Included (Heading hidden if no data)
Histopathology Observations:	Included (Heading hidden if no data)
Gross Items Included:	NVL Tissues; NE Tissues;
Histo Items Included:	NVL Tissues; NE Tissues;

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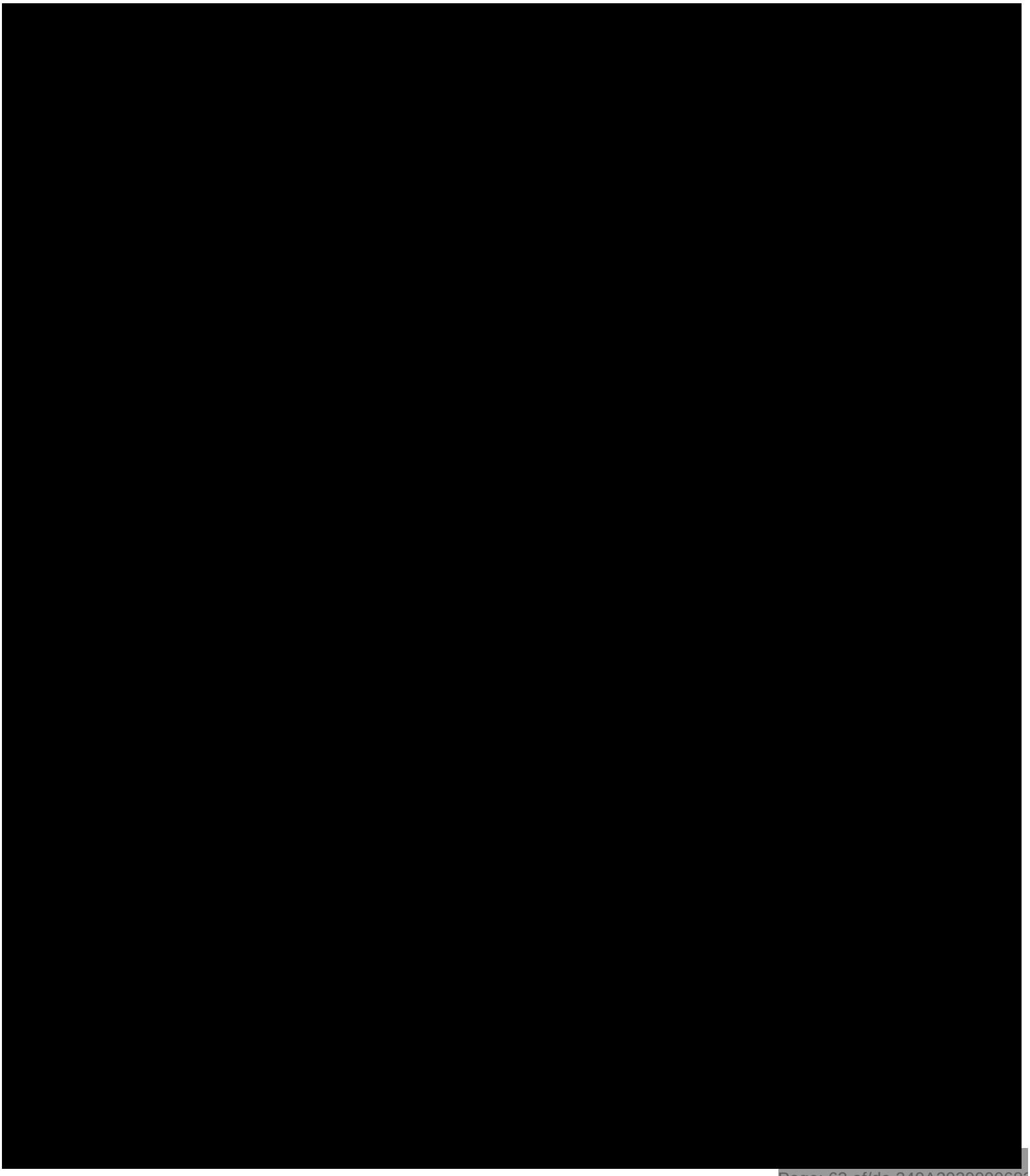

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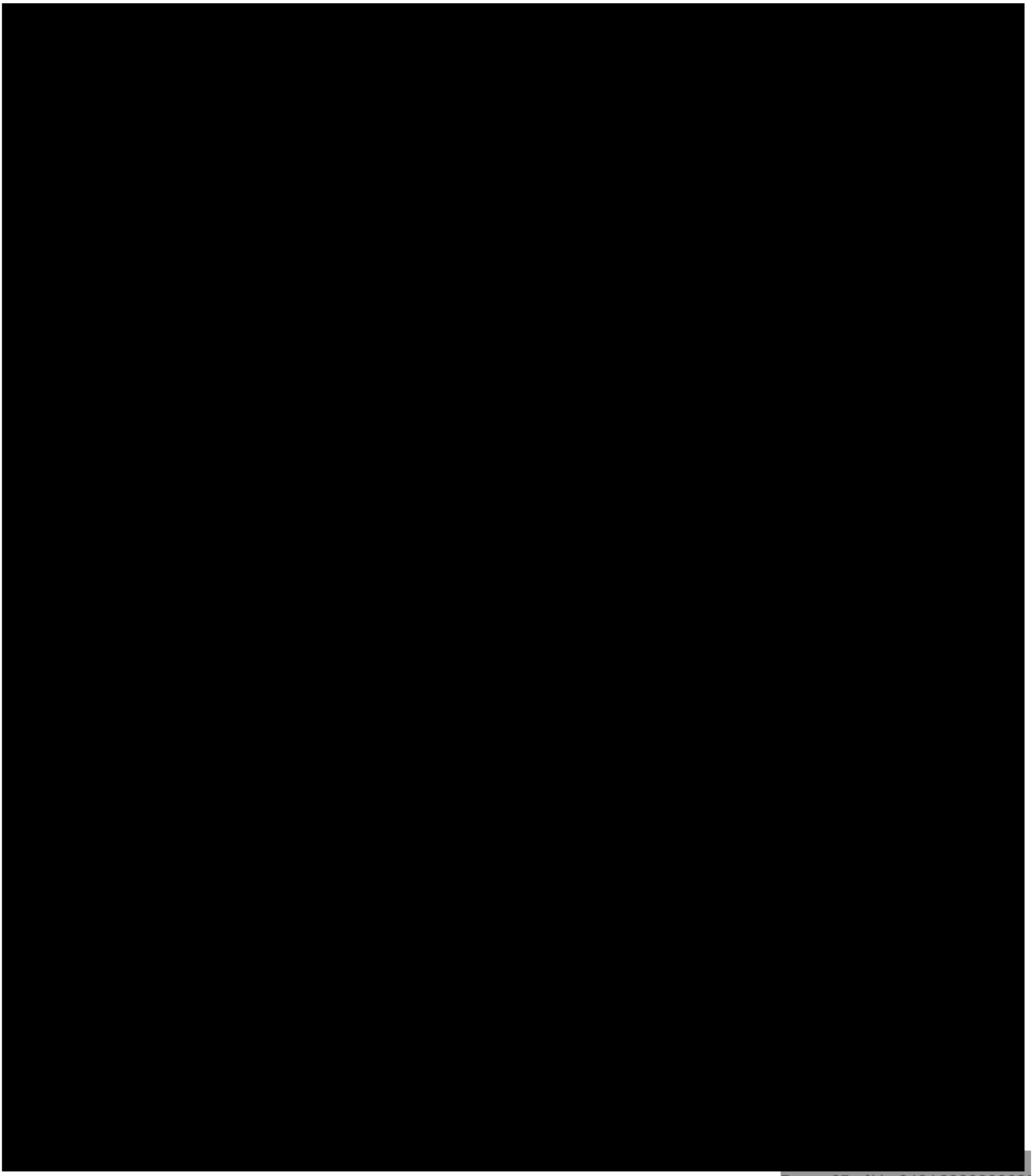

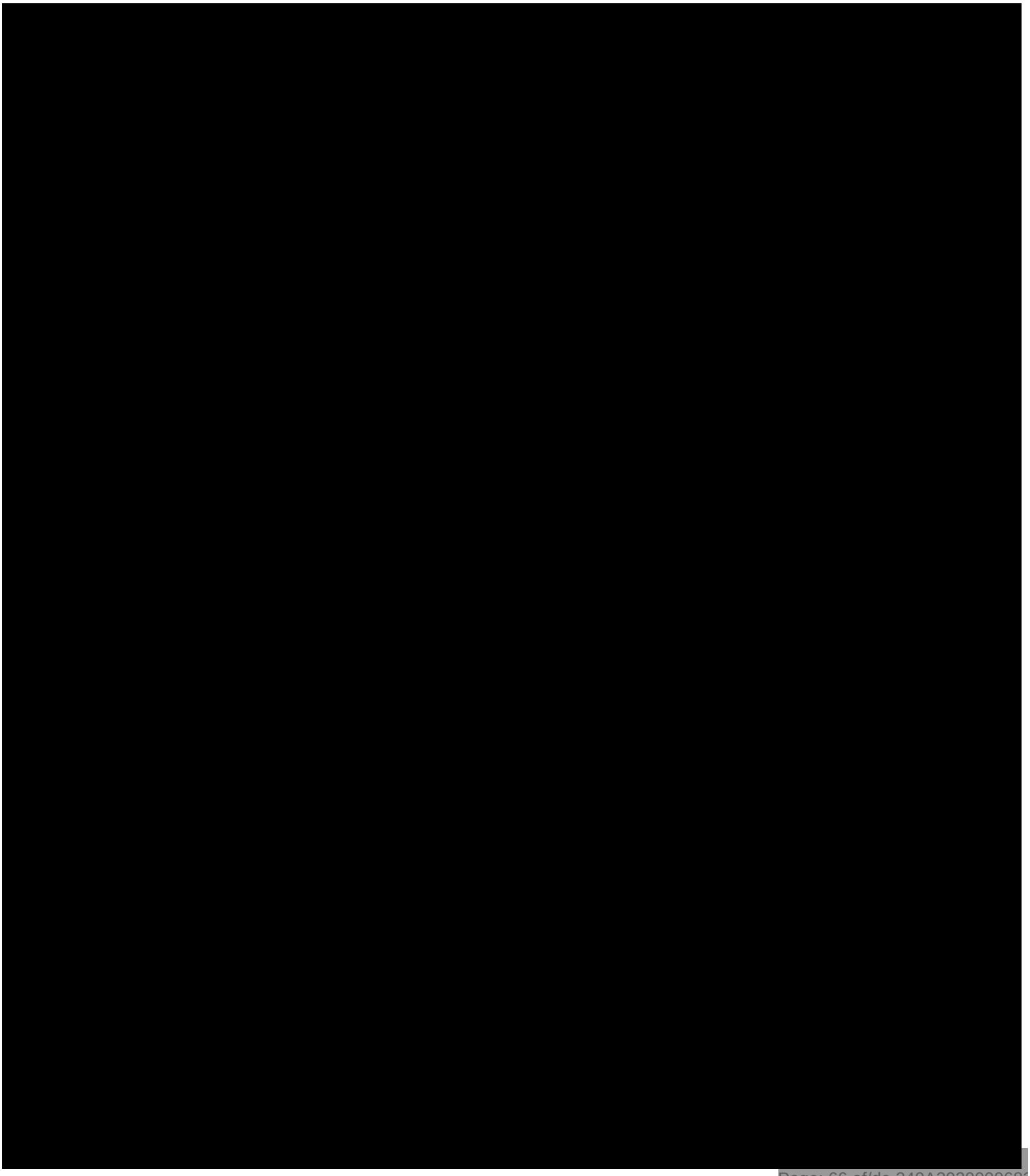

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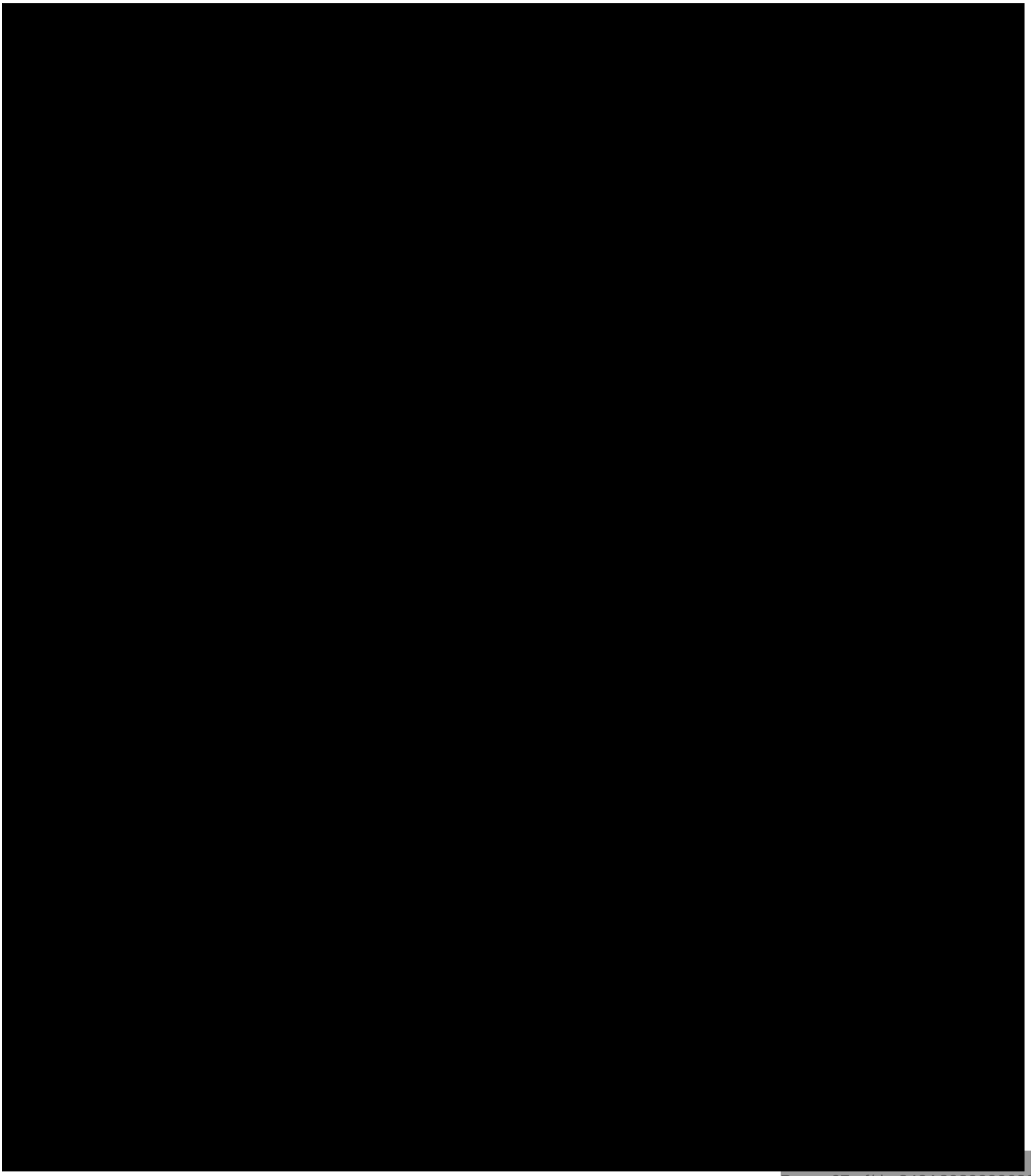

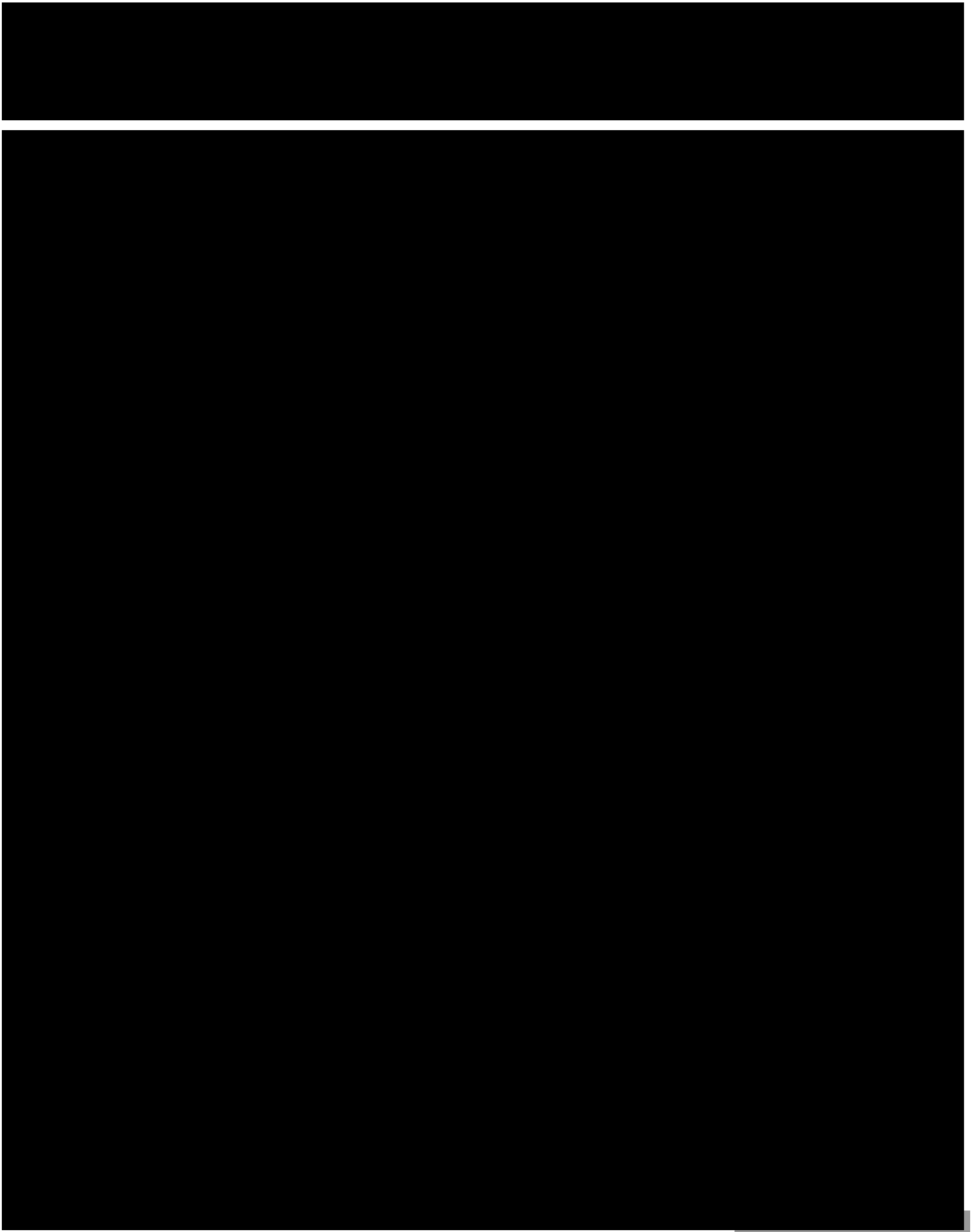

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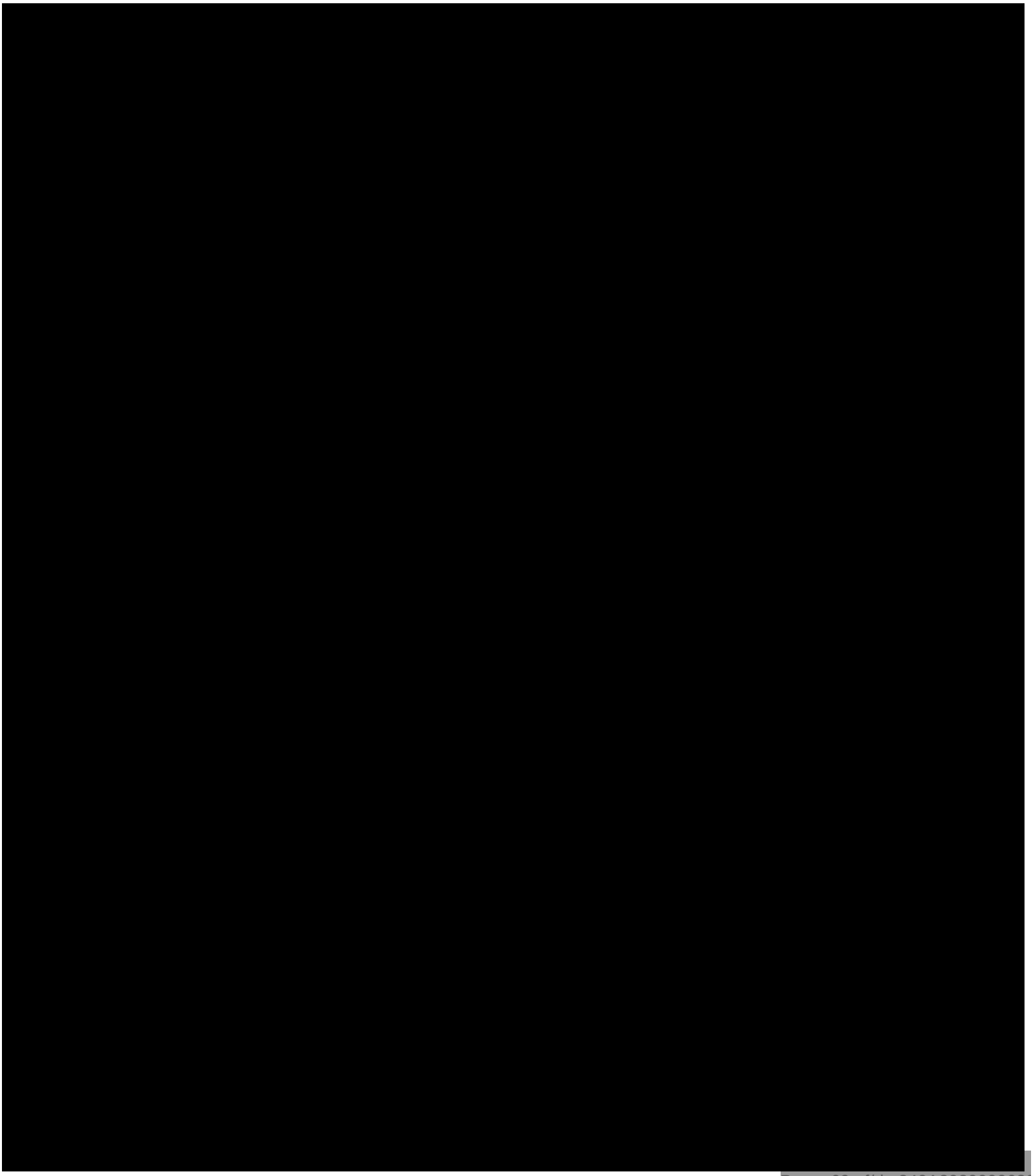

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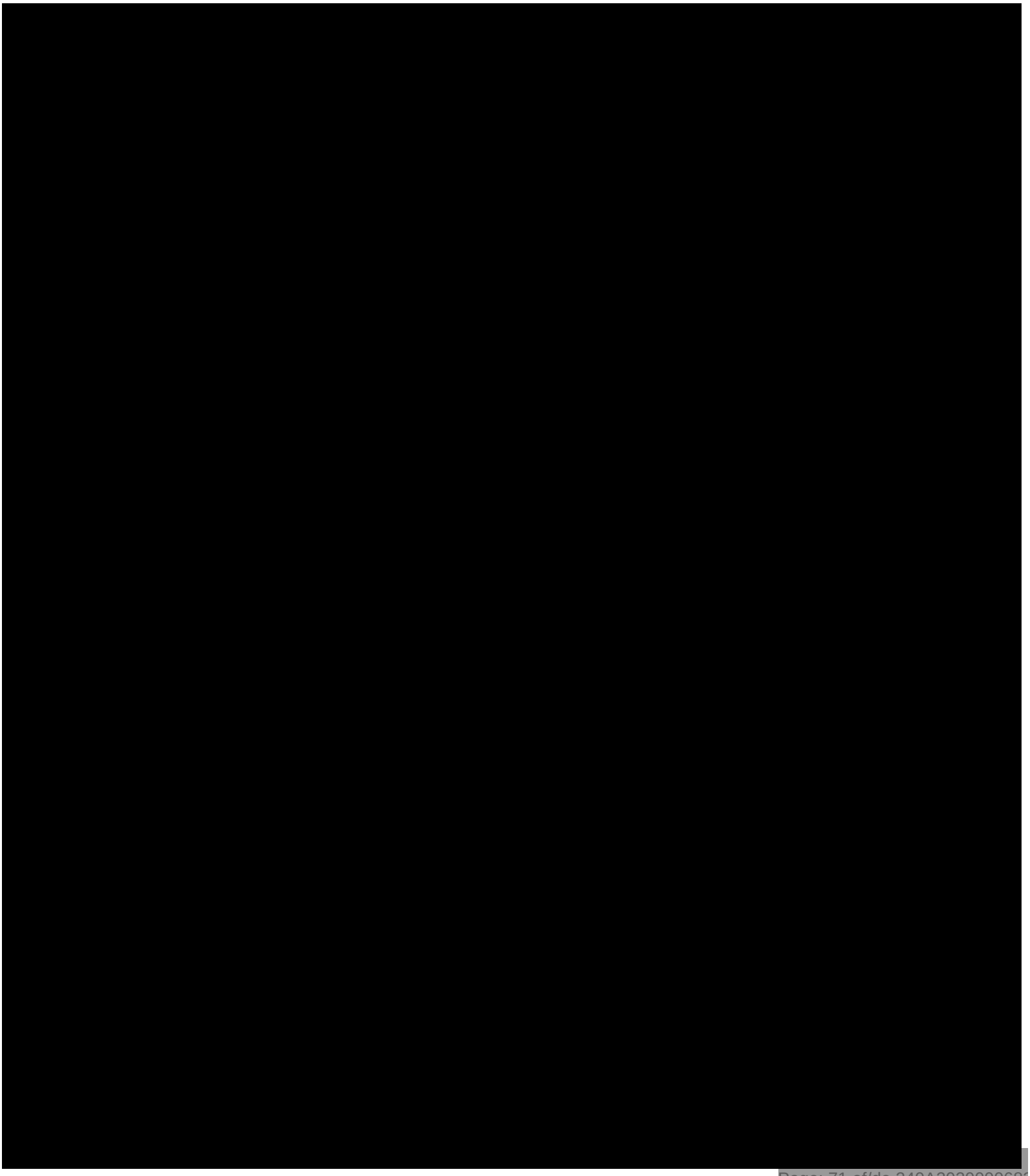

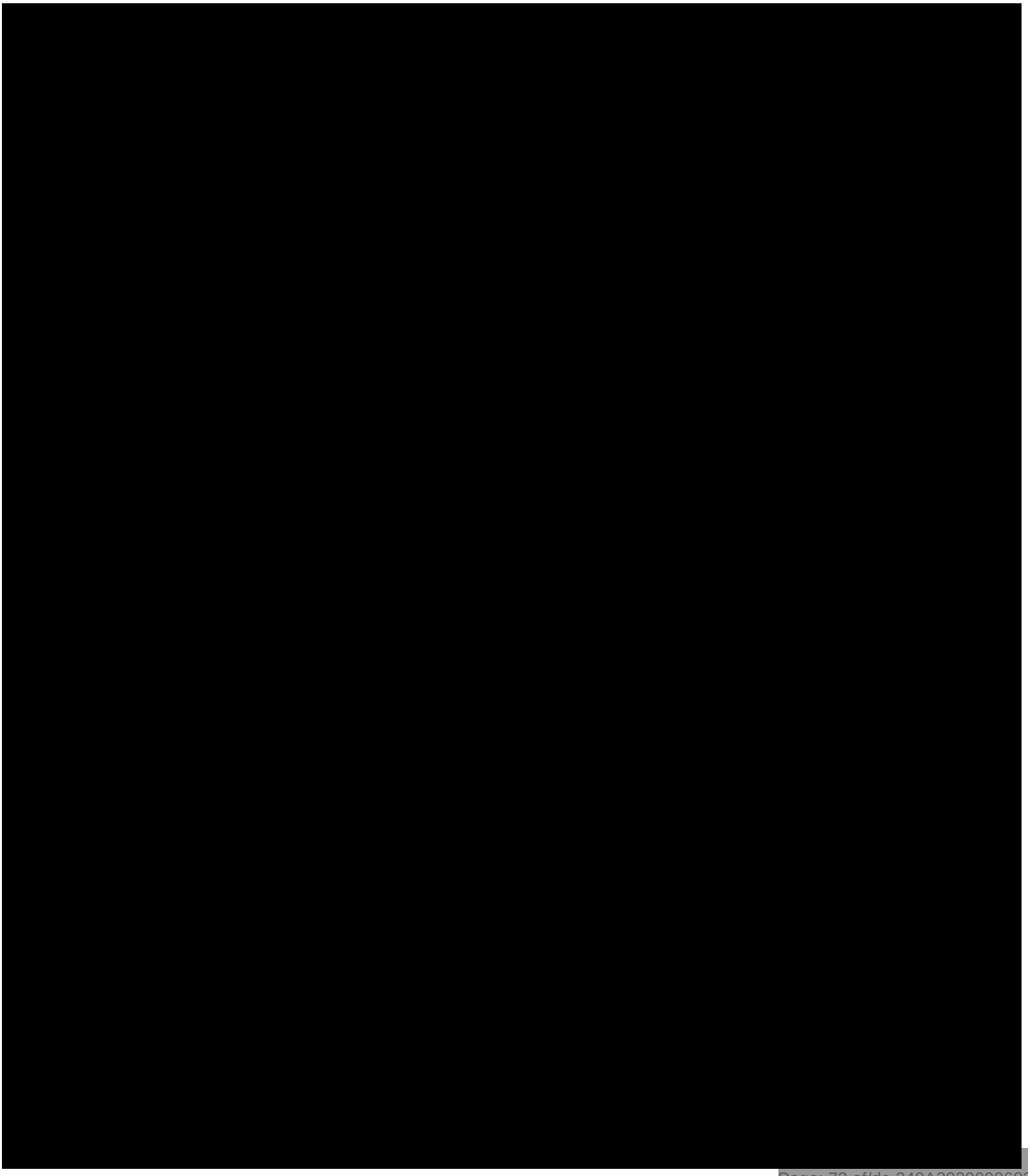

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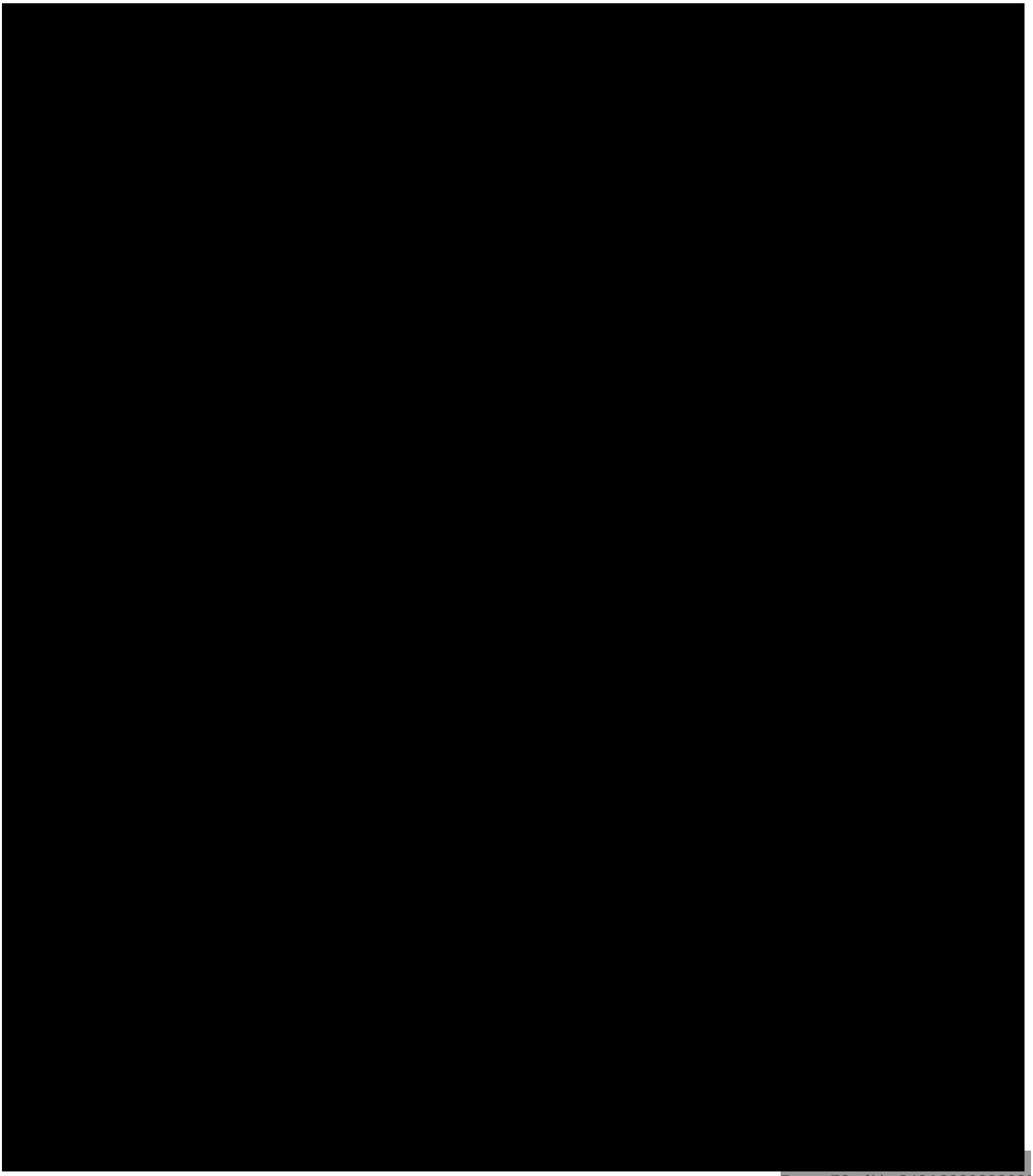

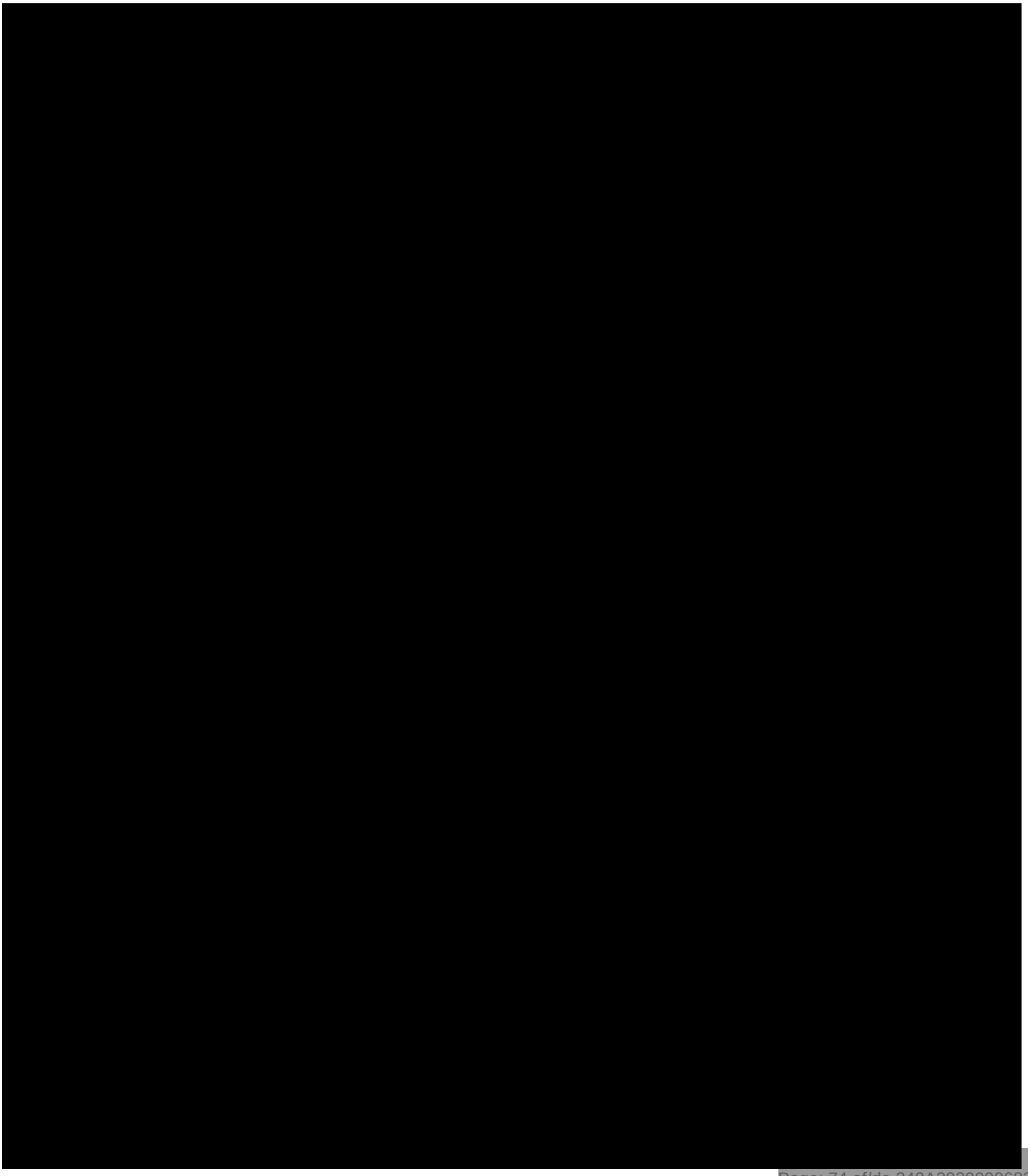

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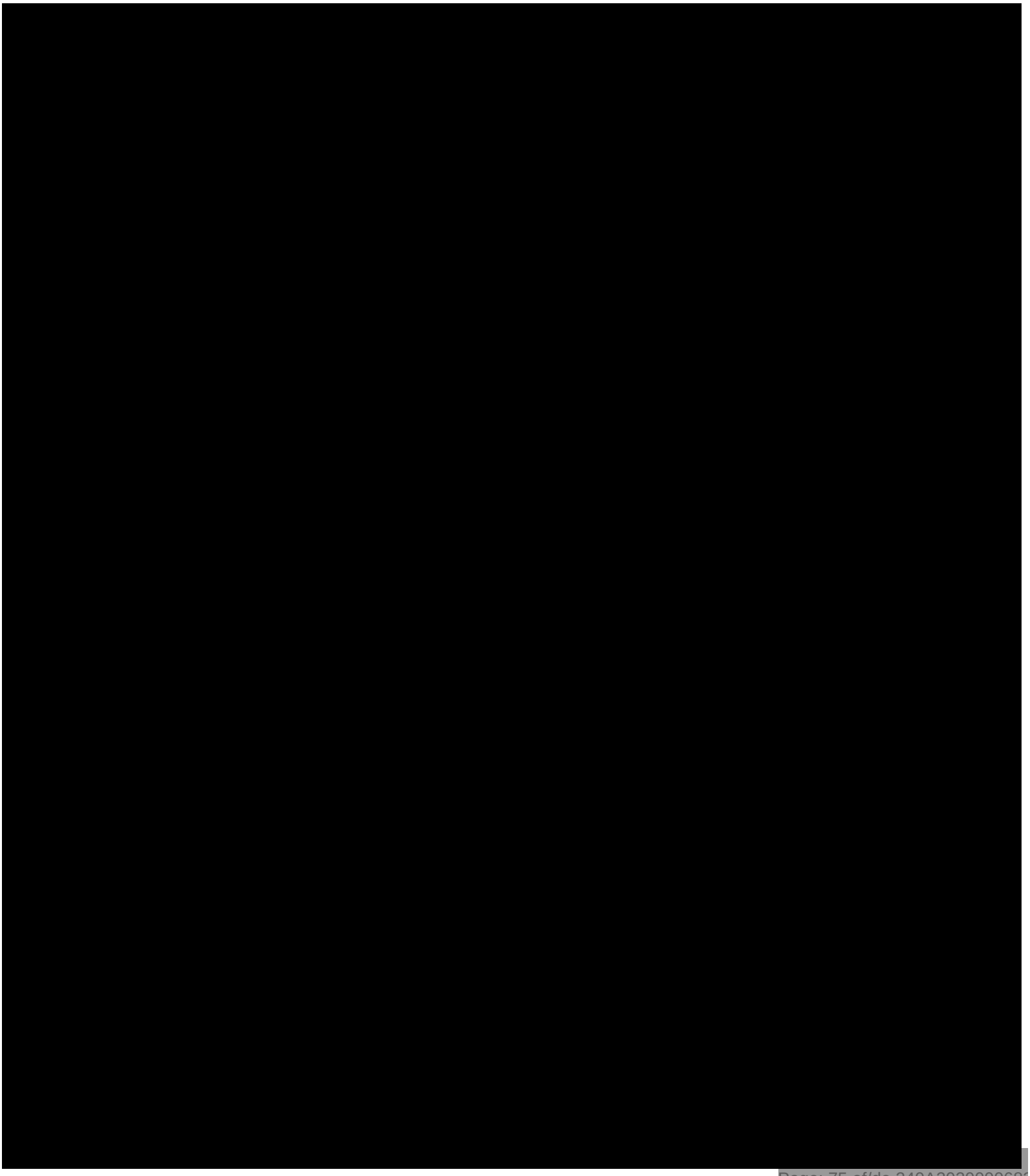

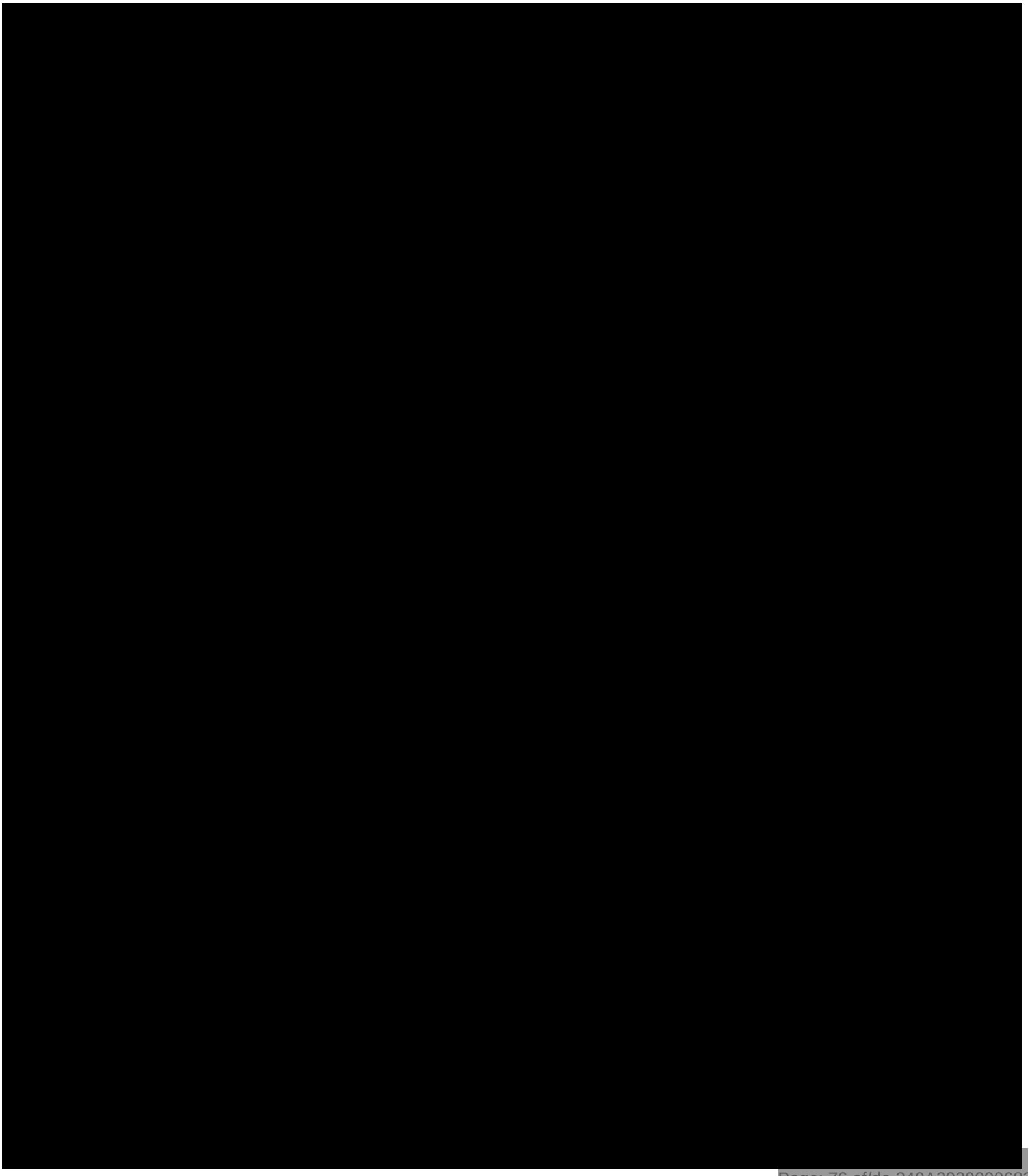

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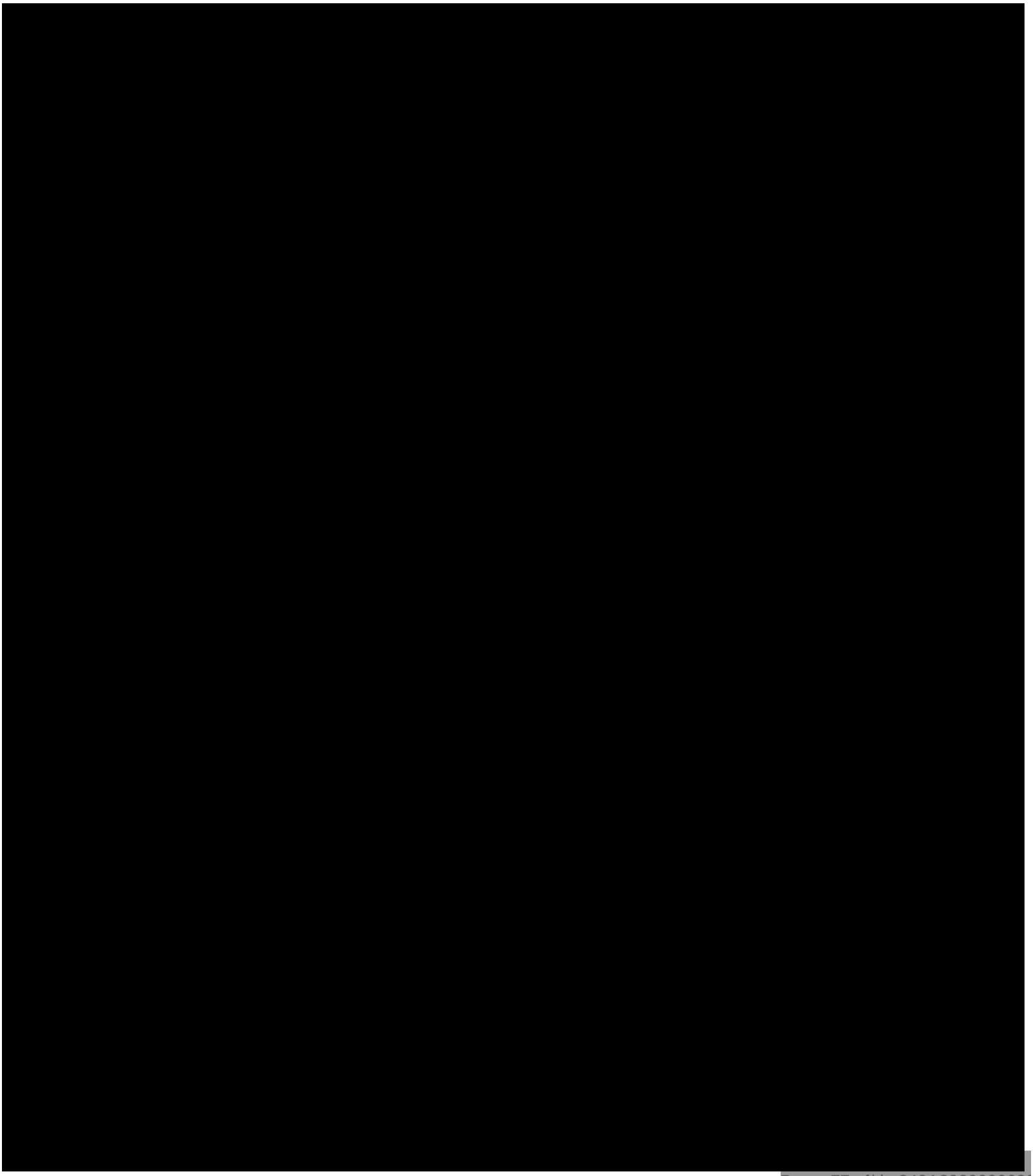

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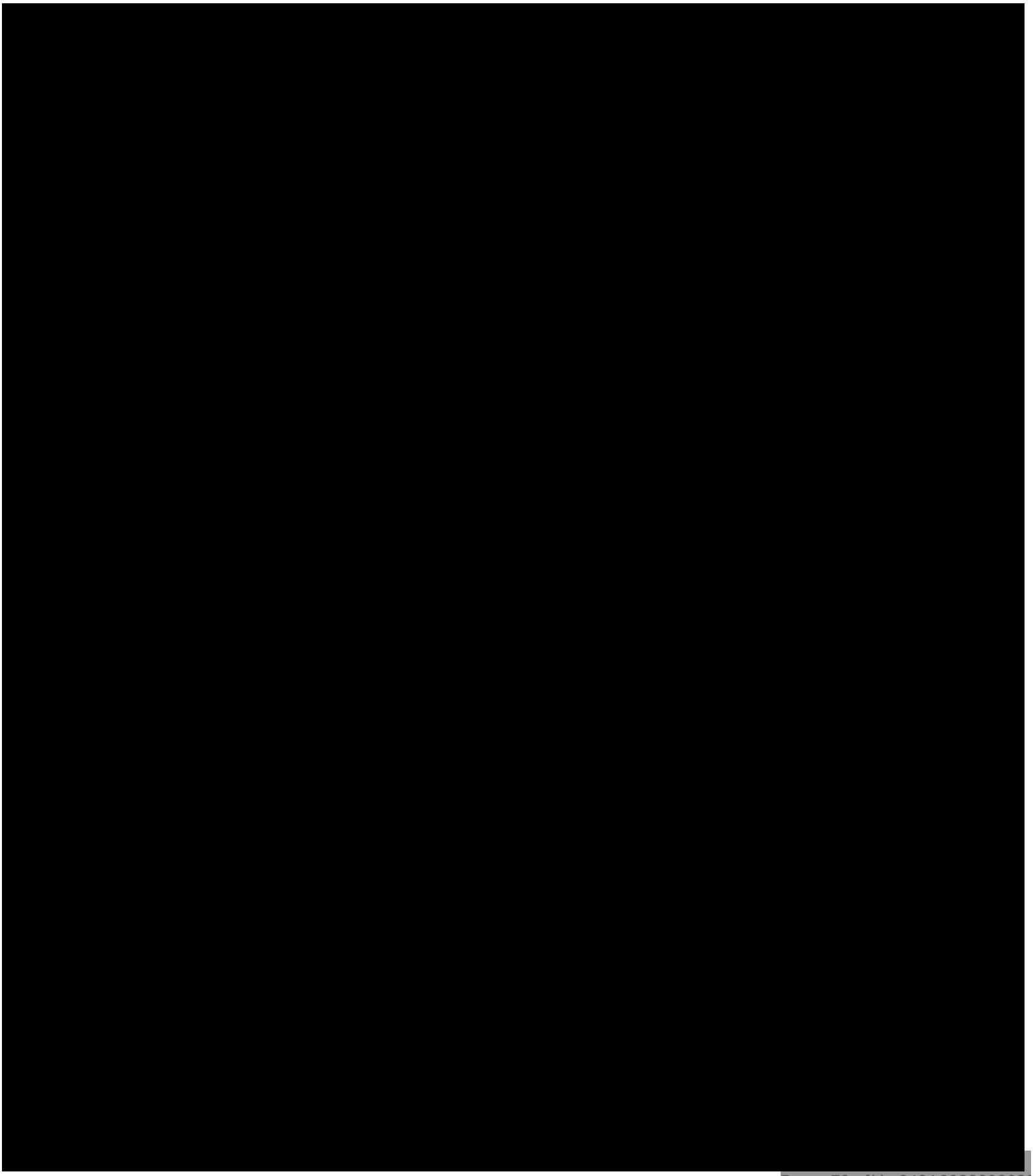

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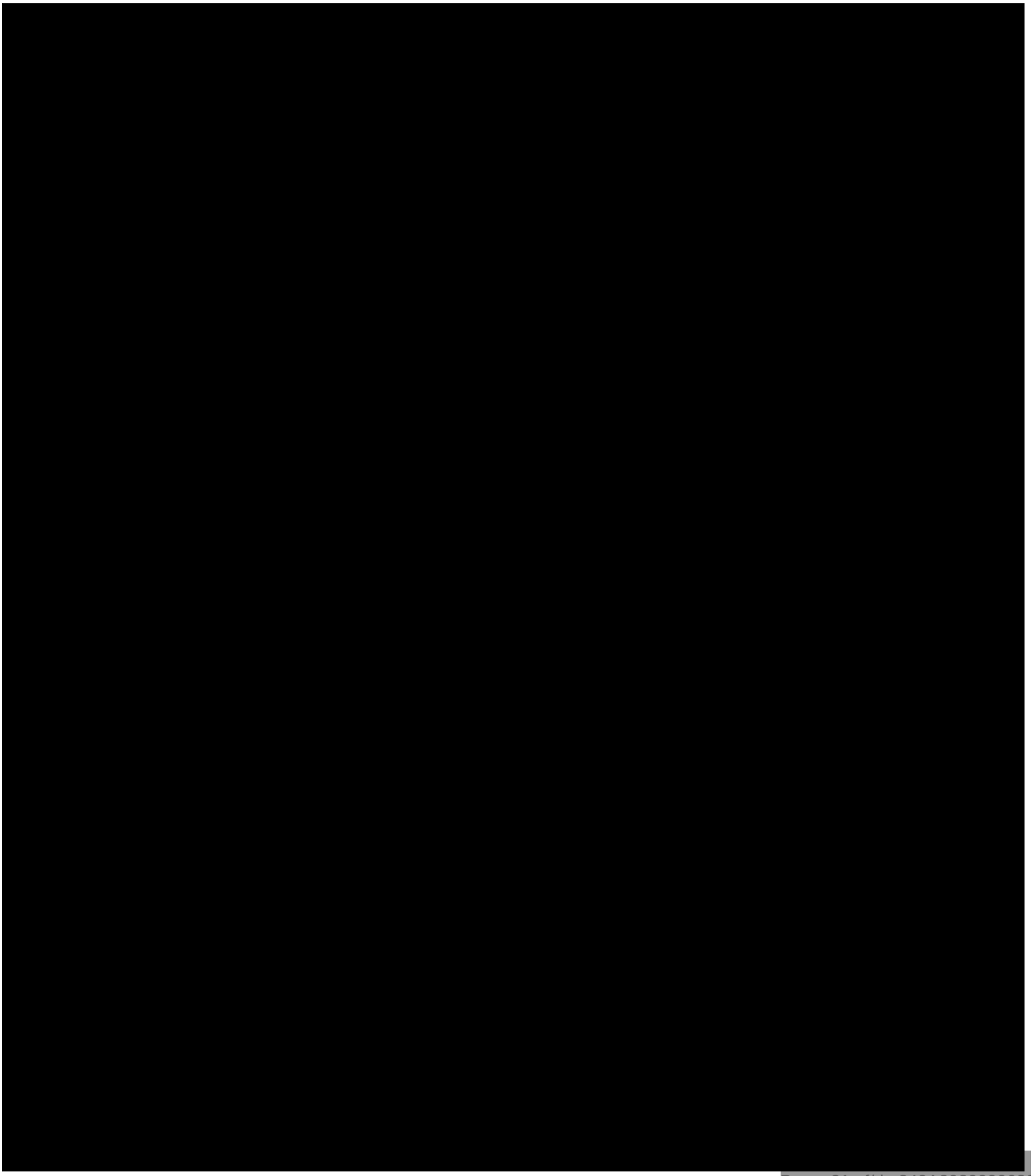

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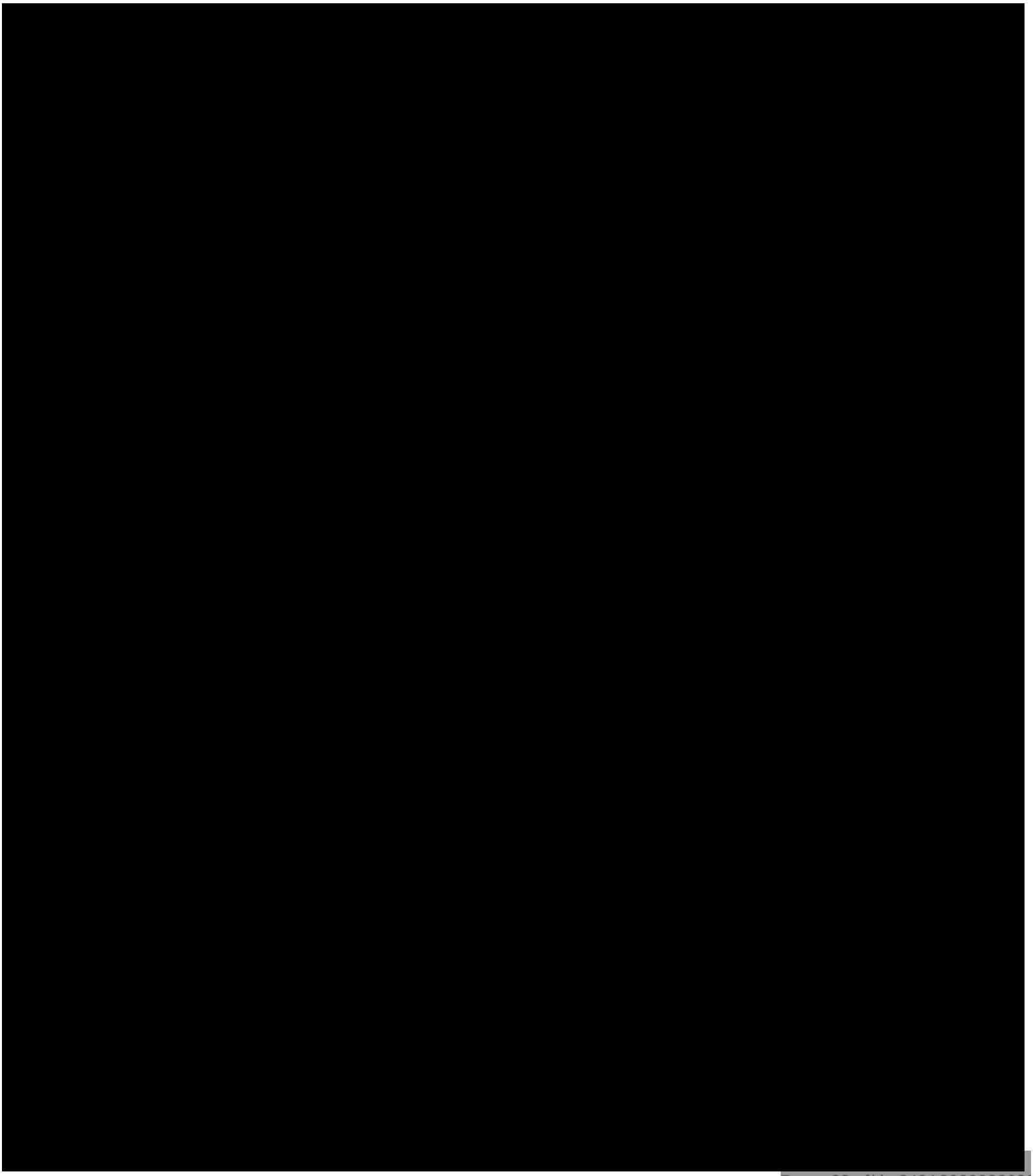

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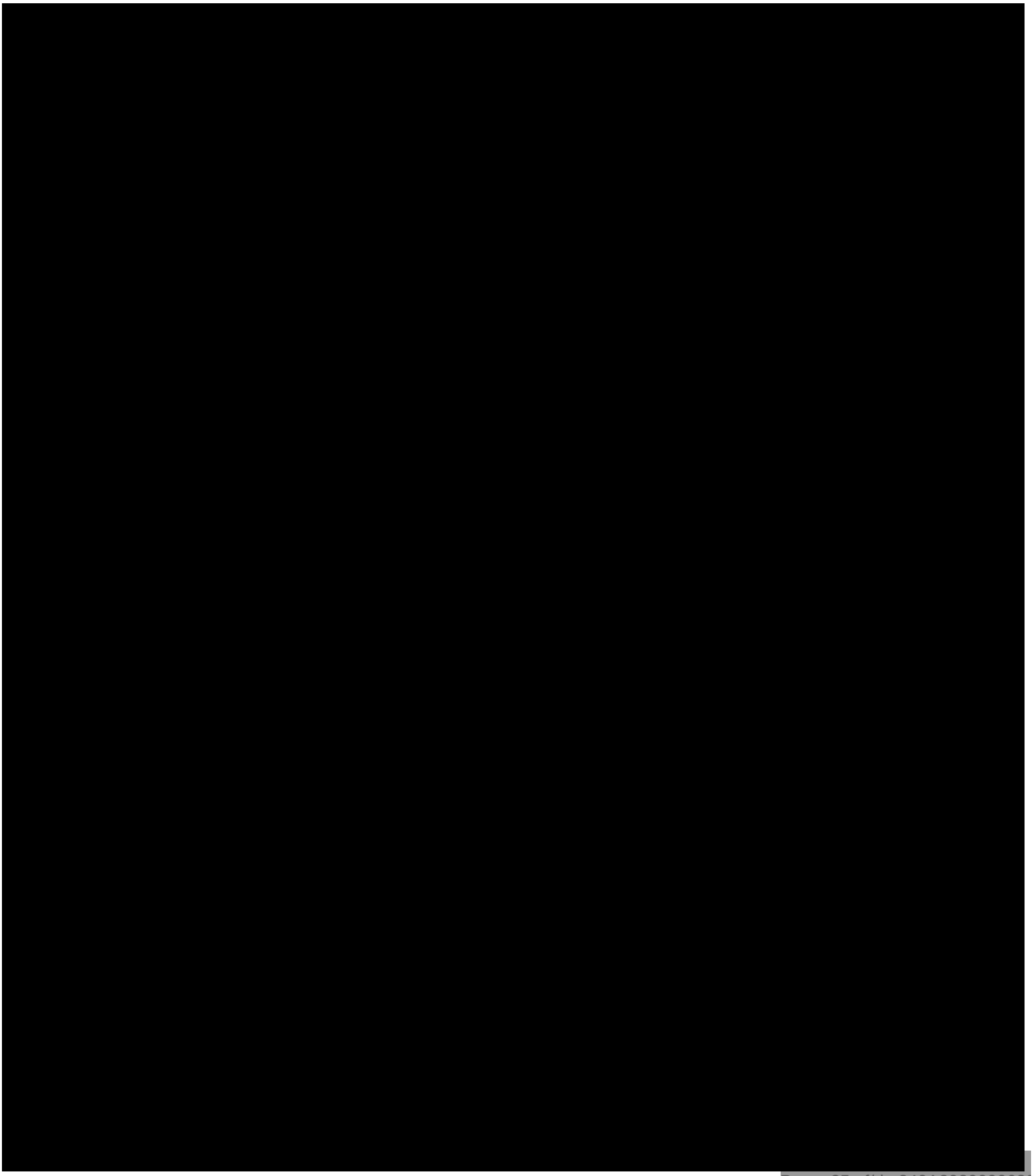

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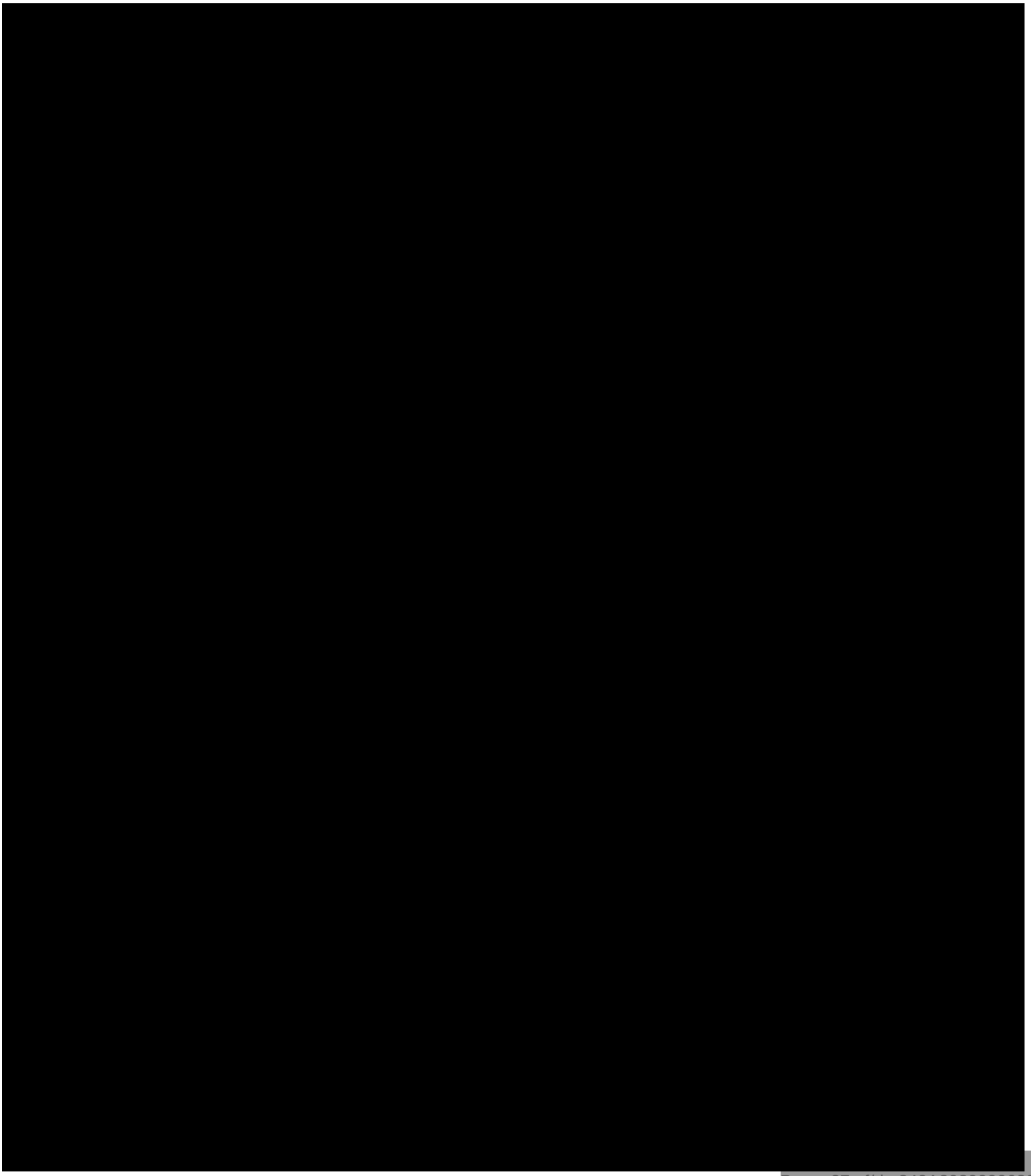

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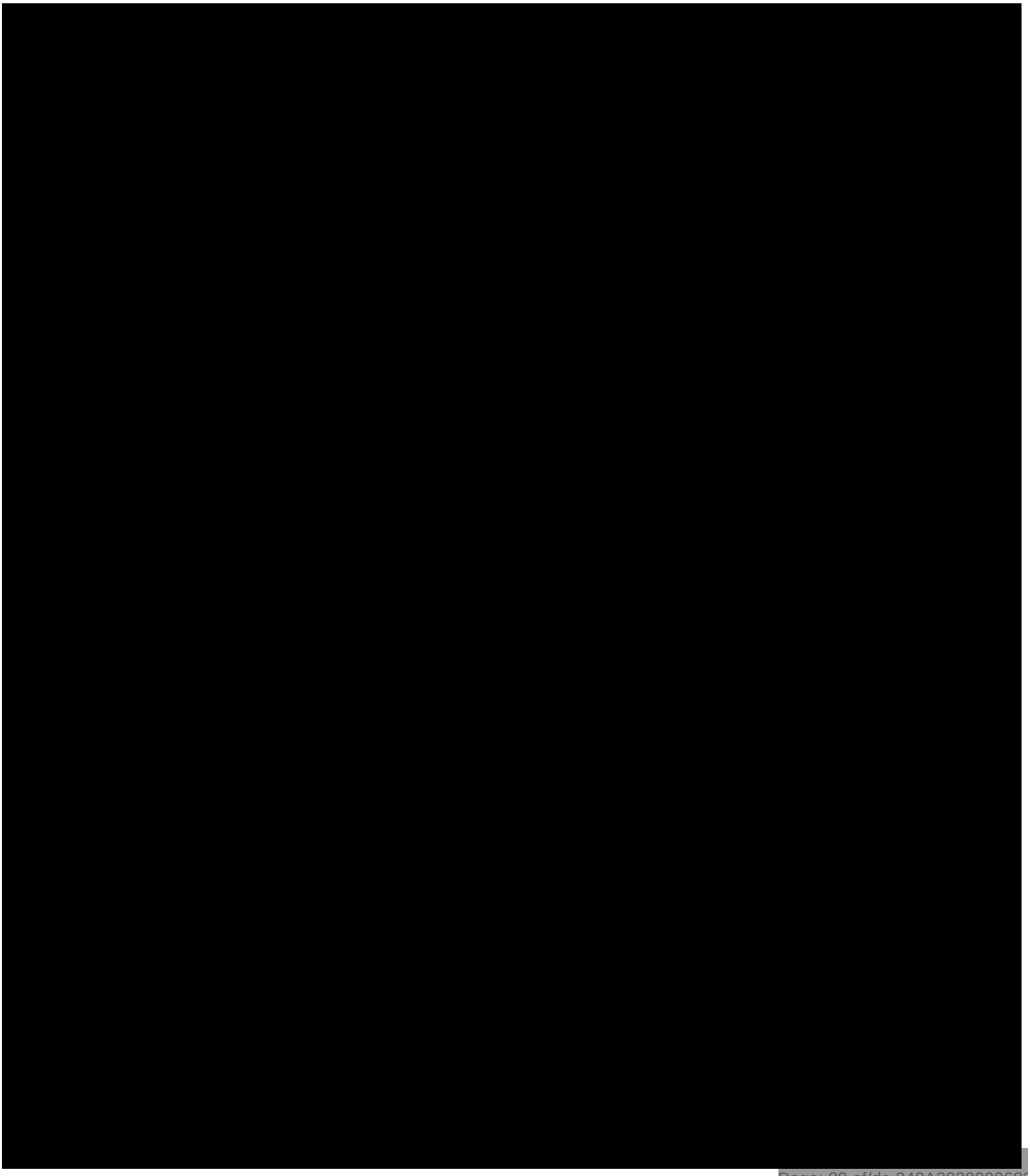

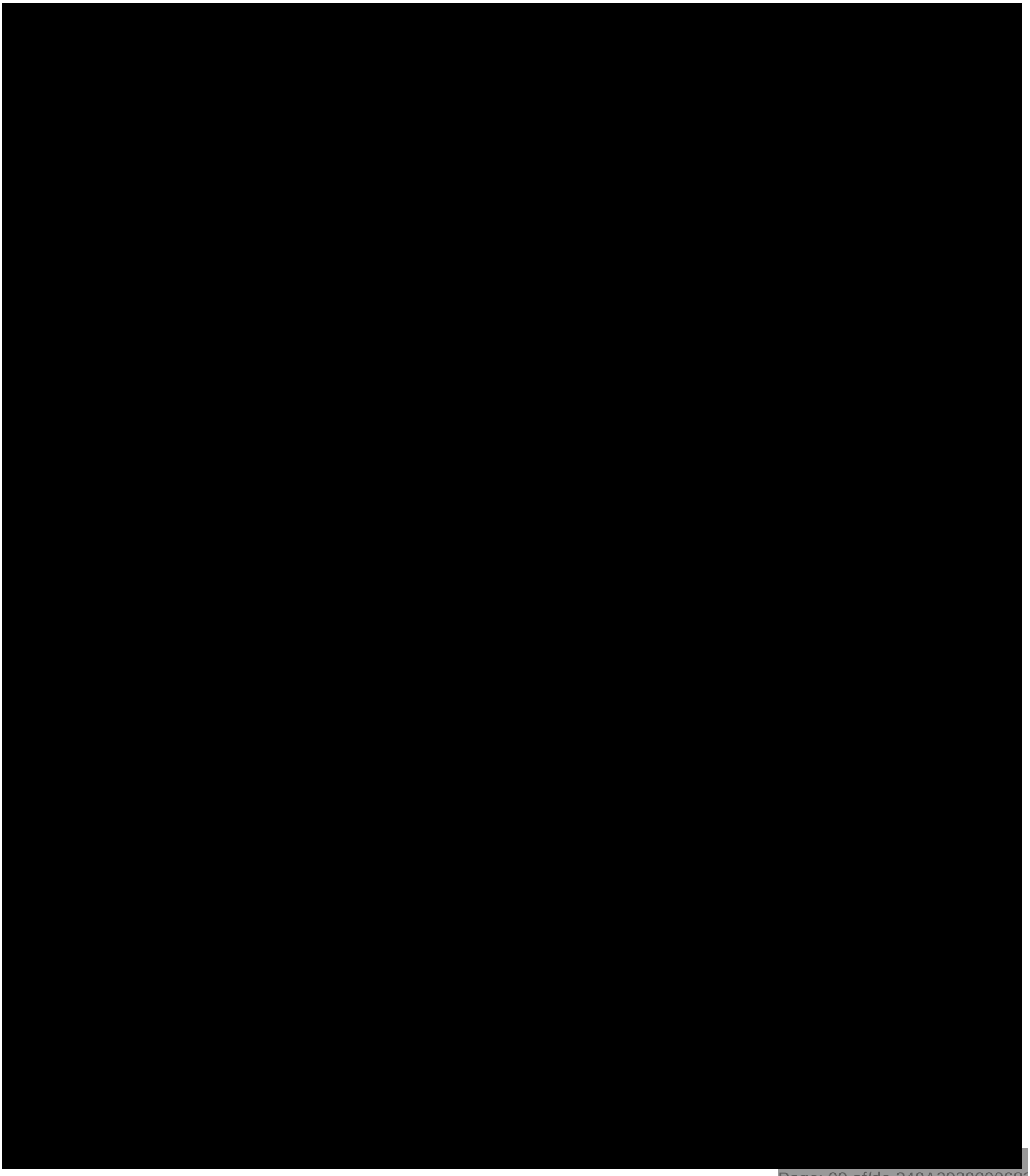

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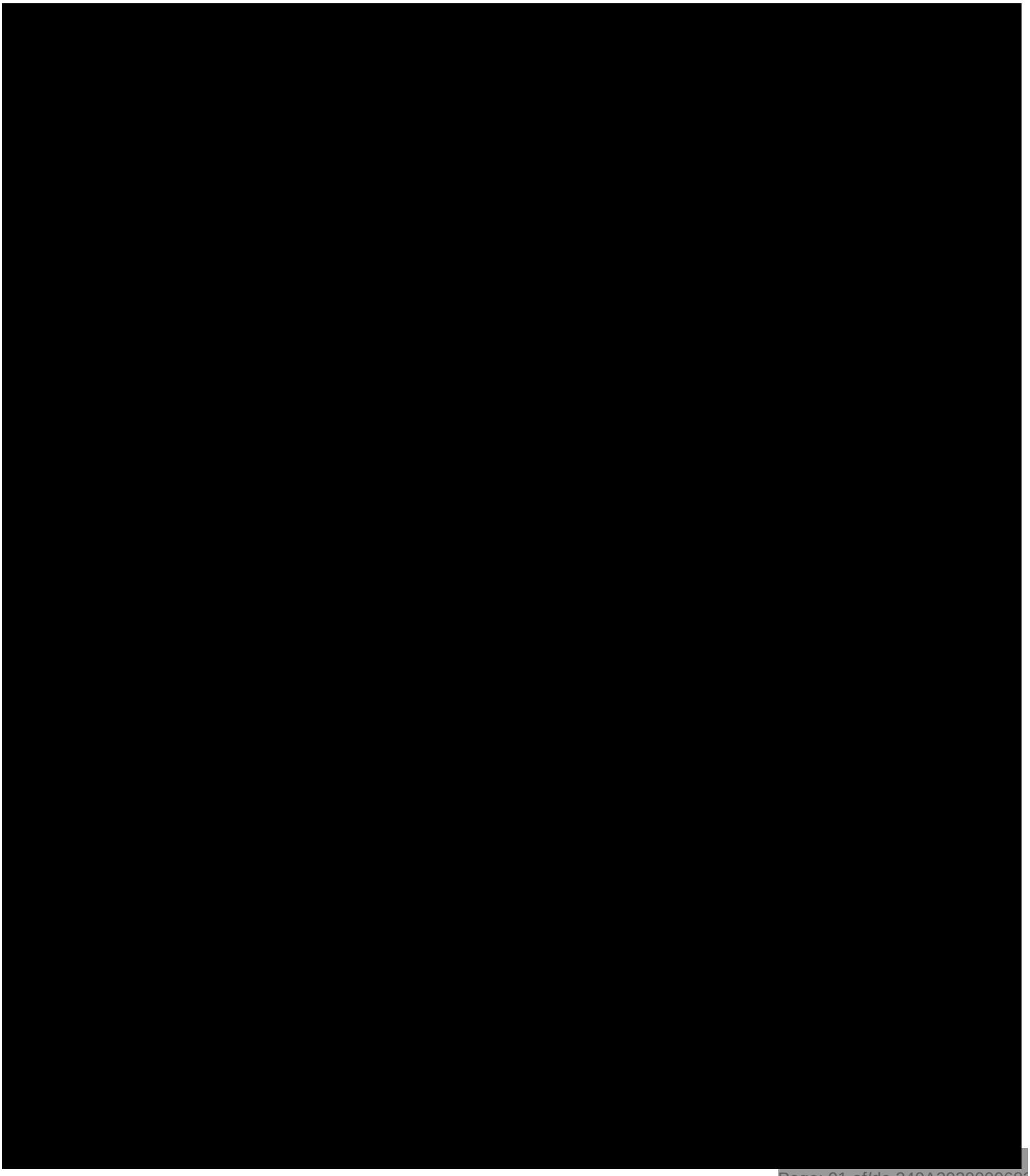

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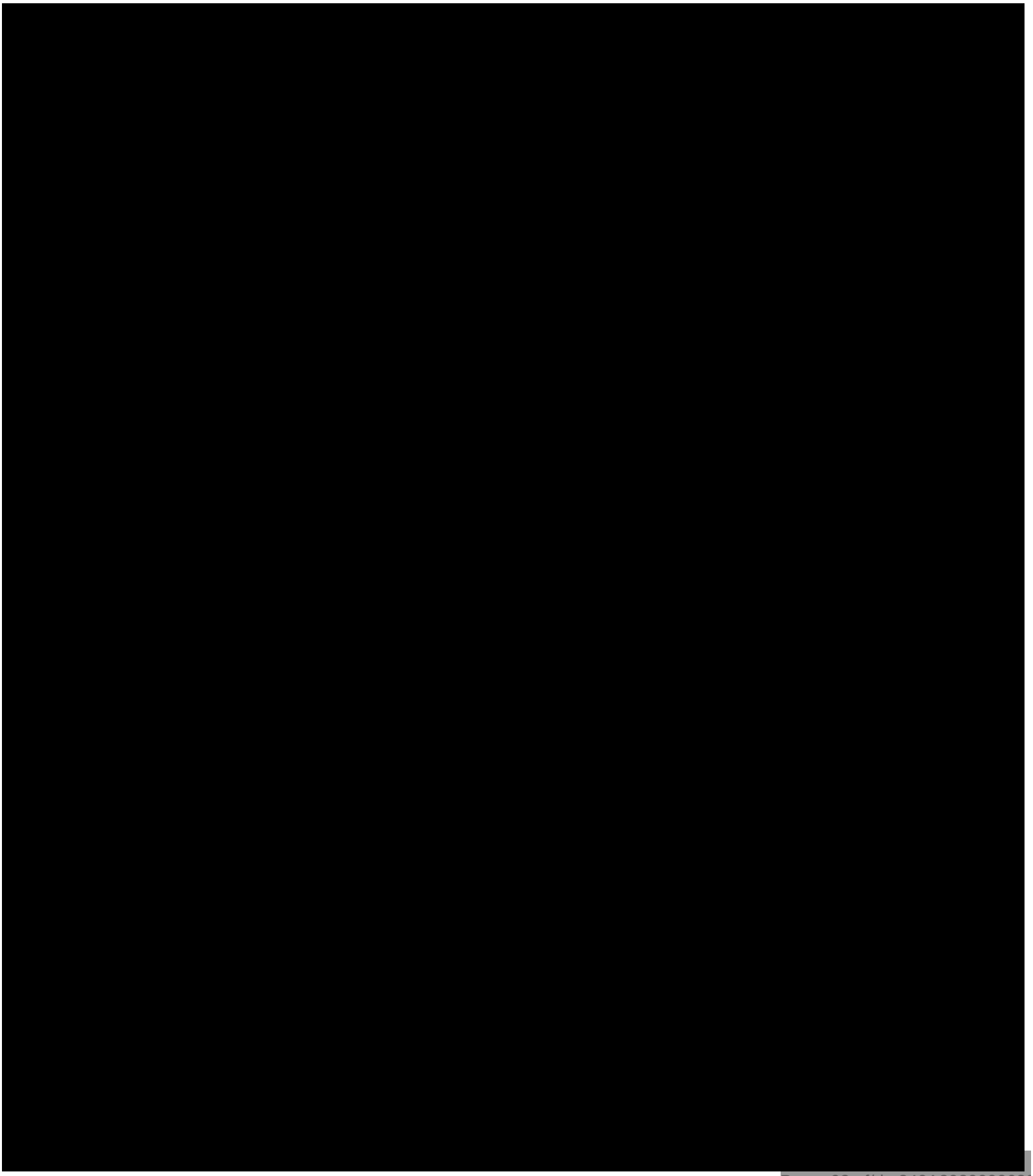

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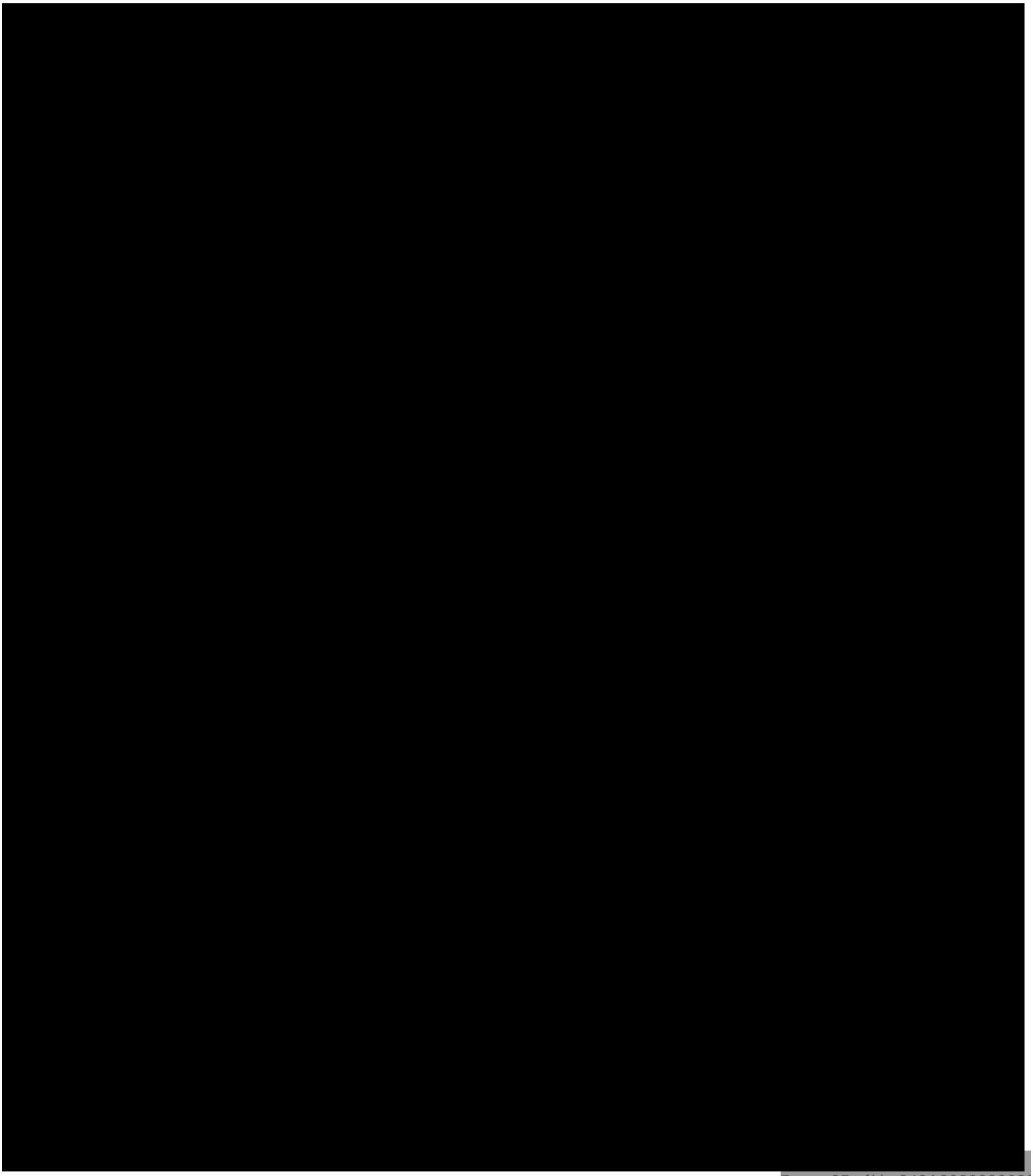

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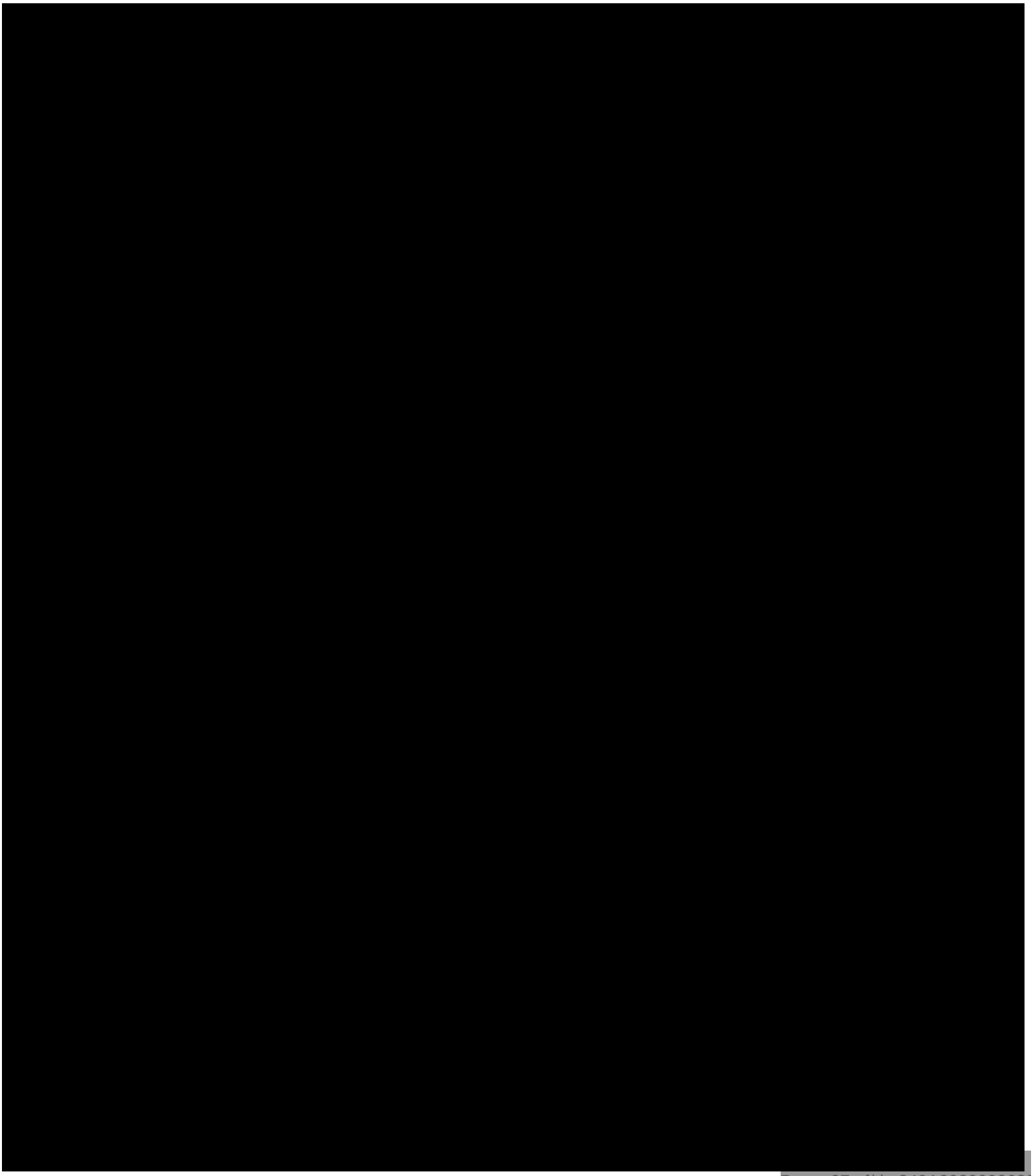

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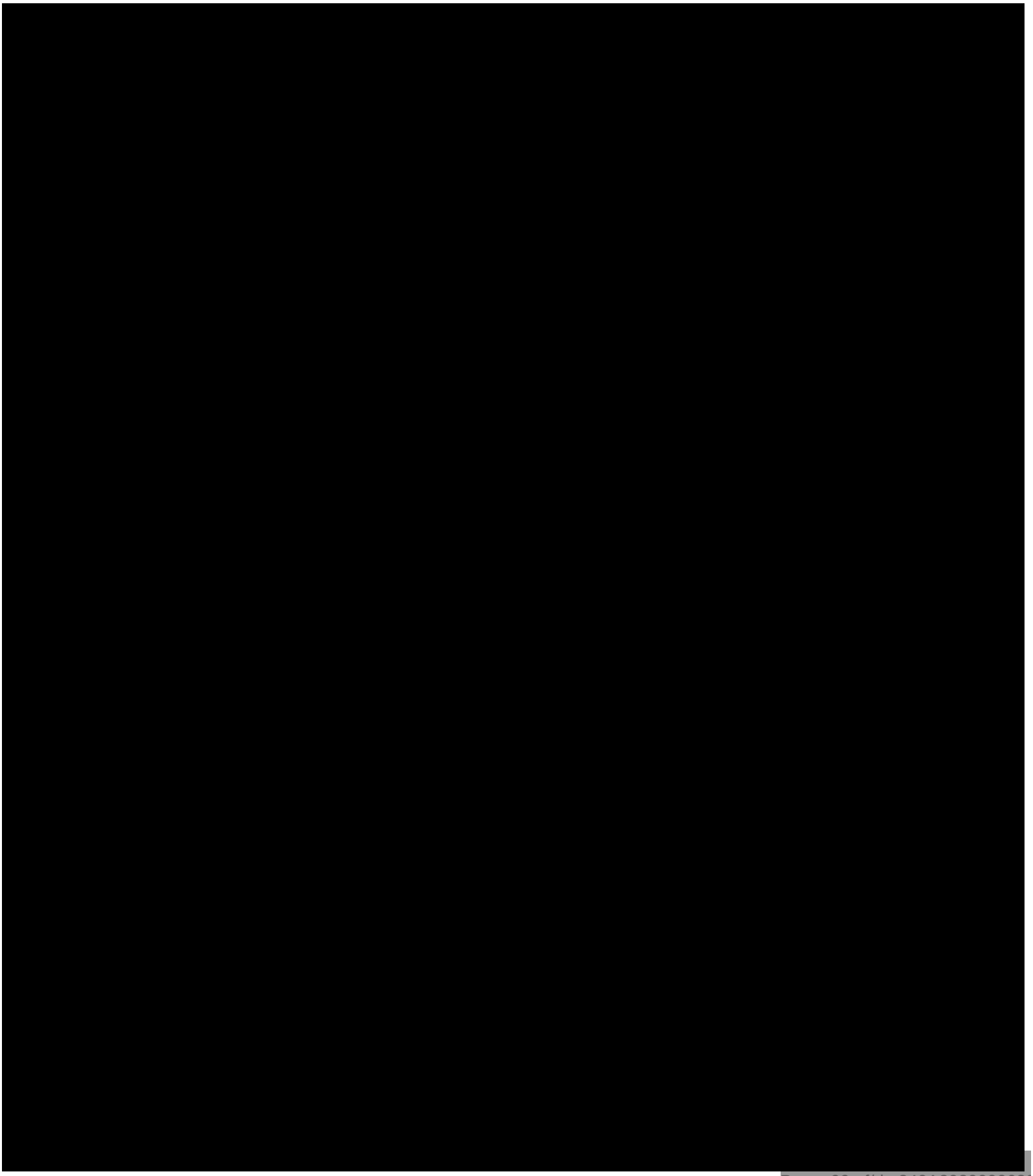

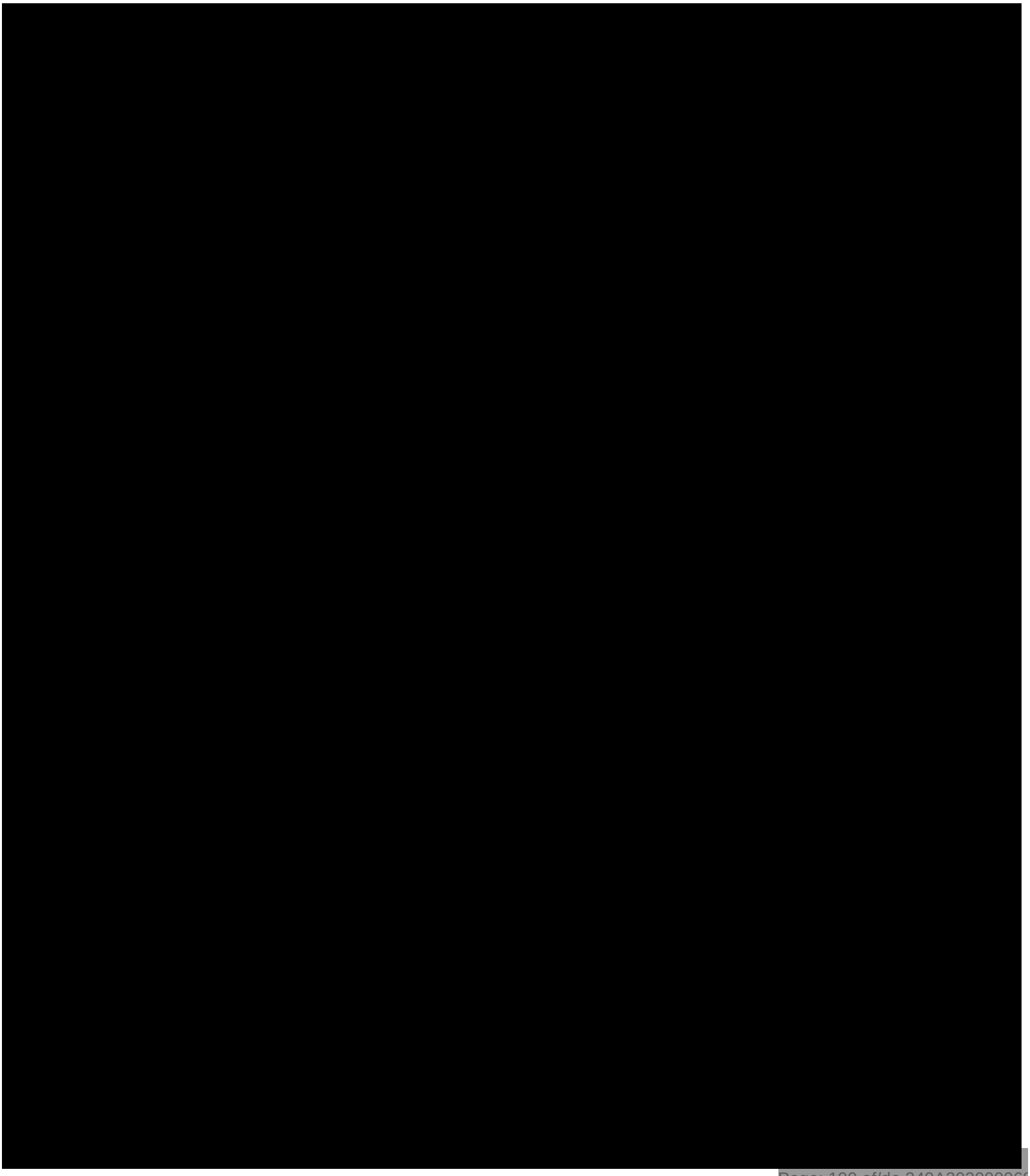

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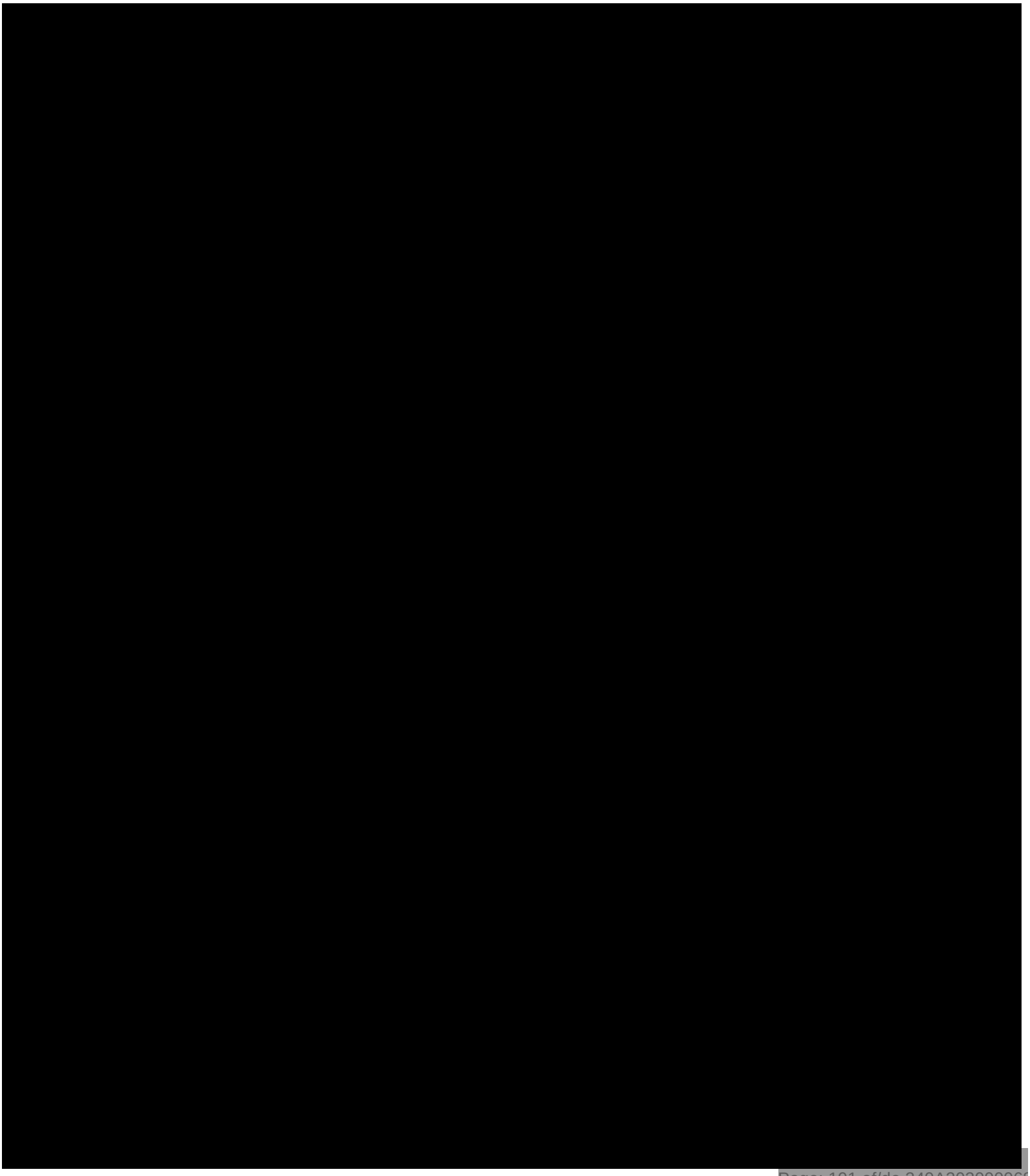

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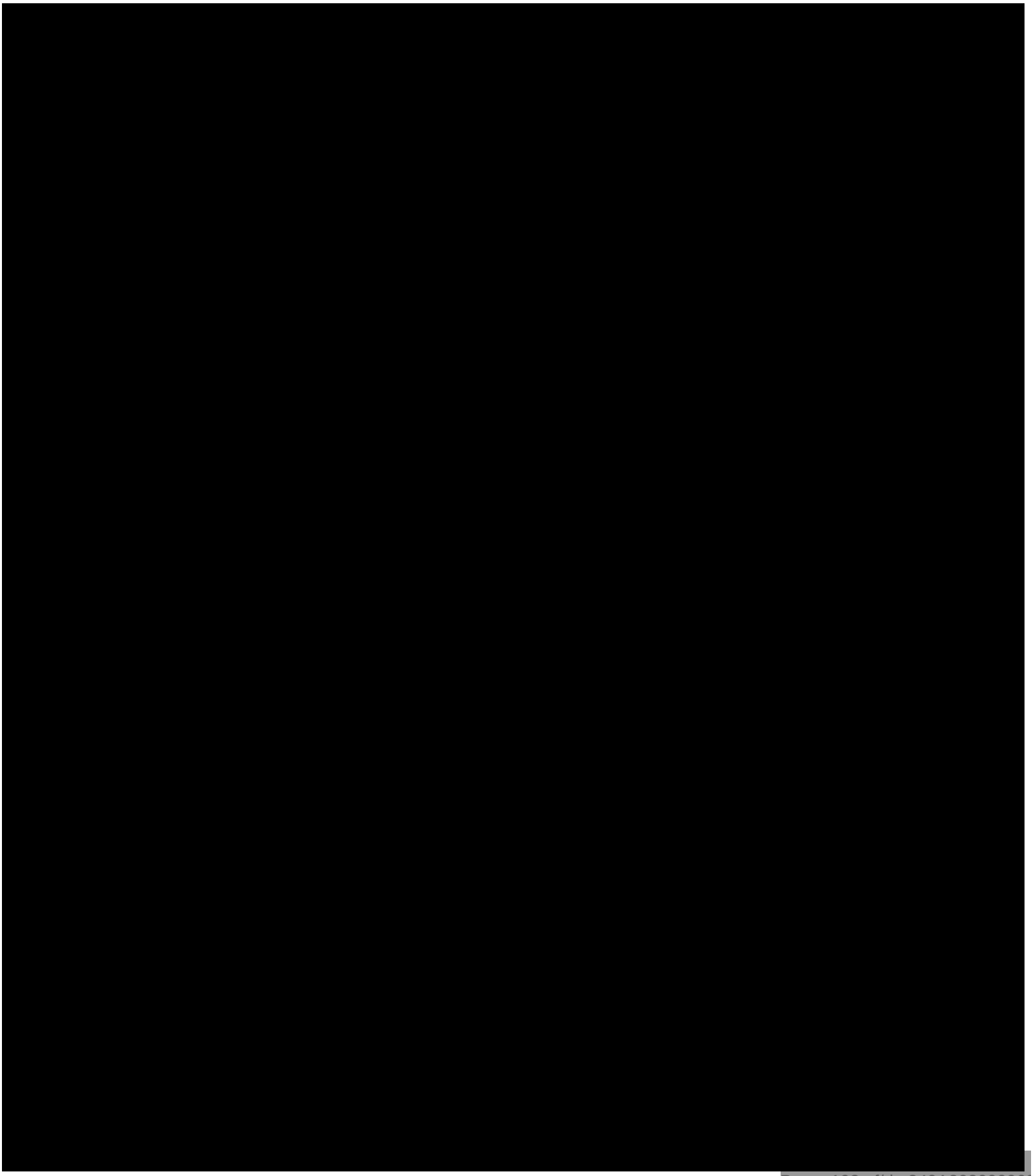

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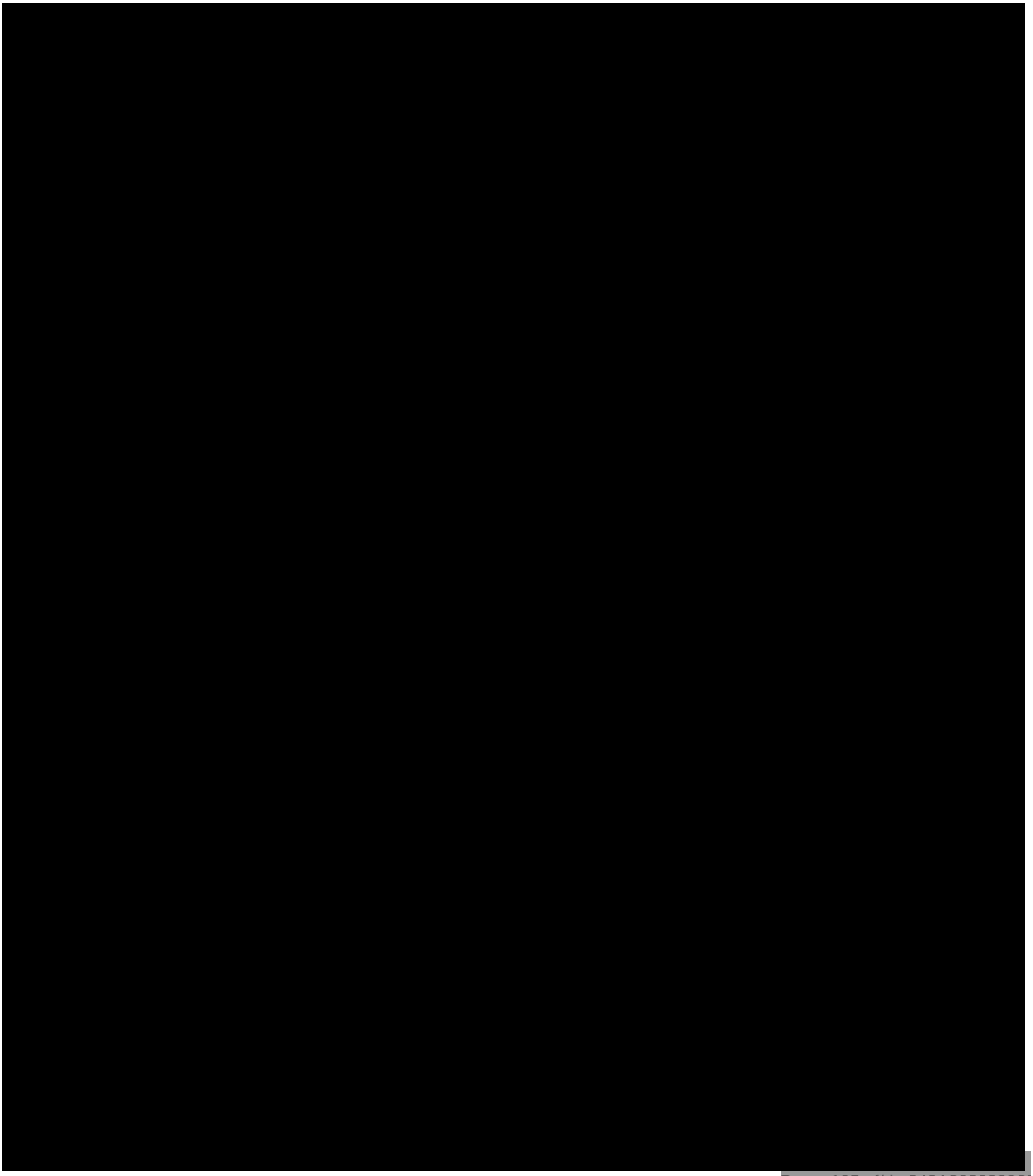

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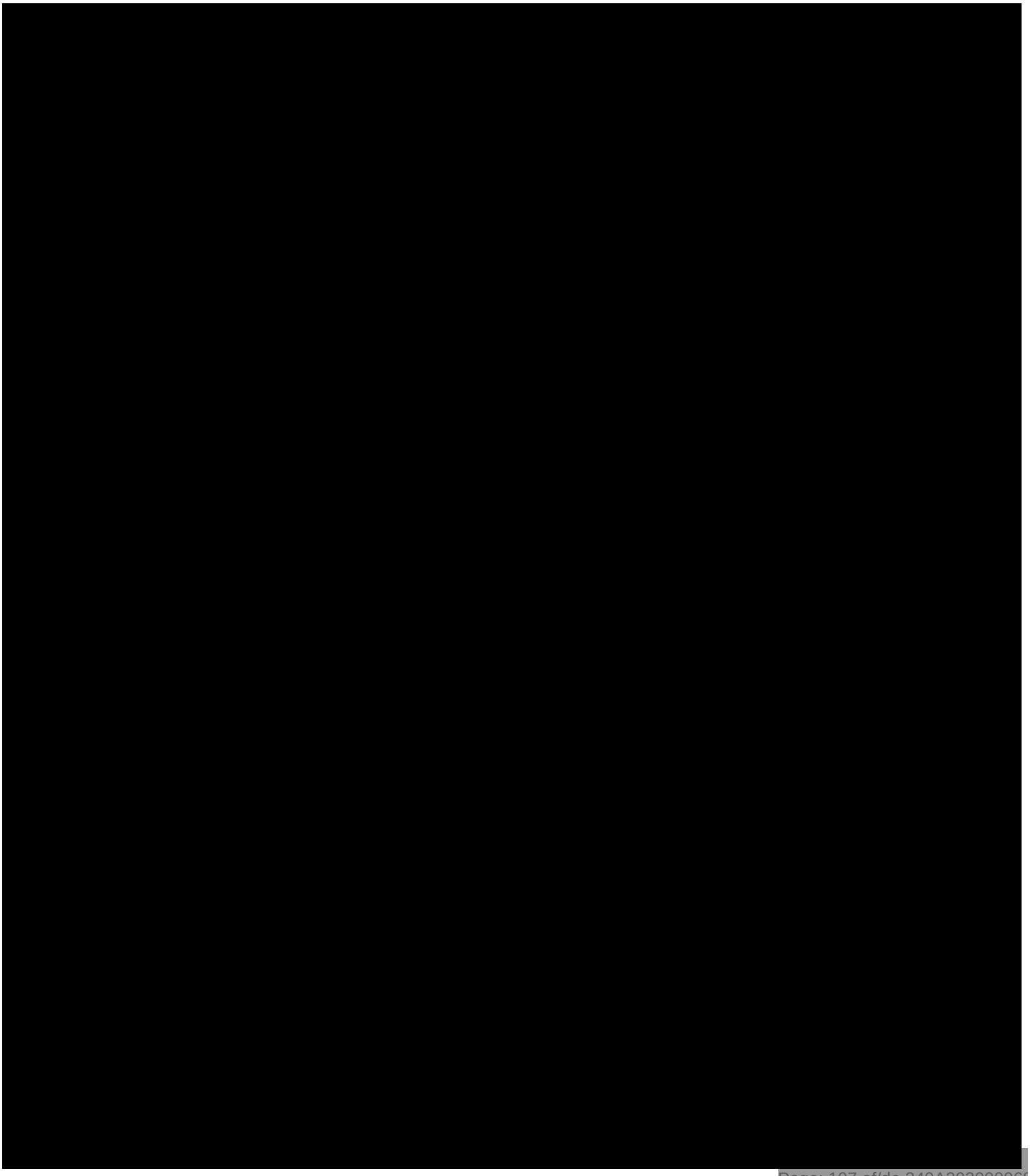

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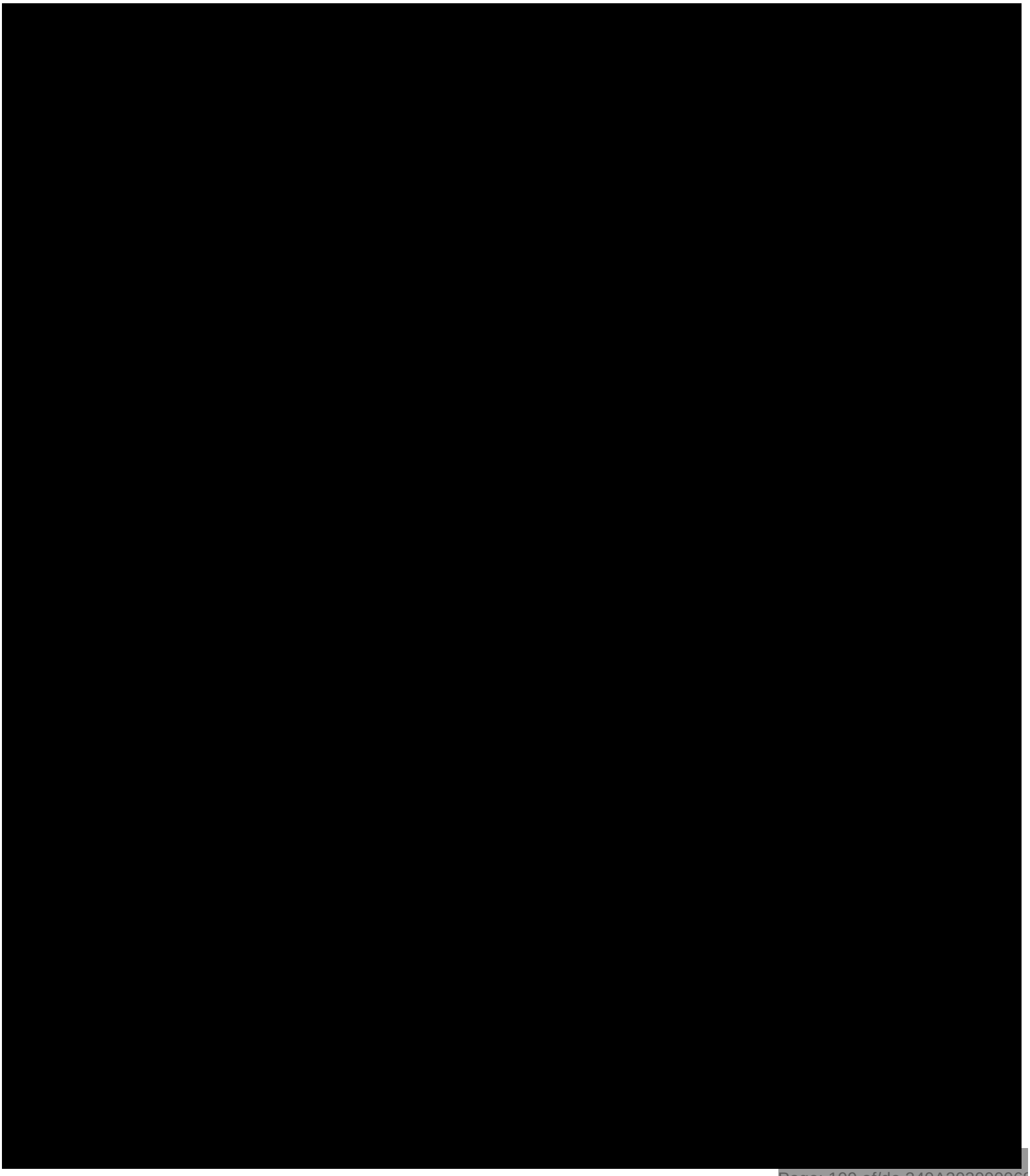

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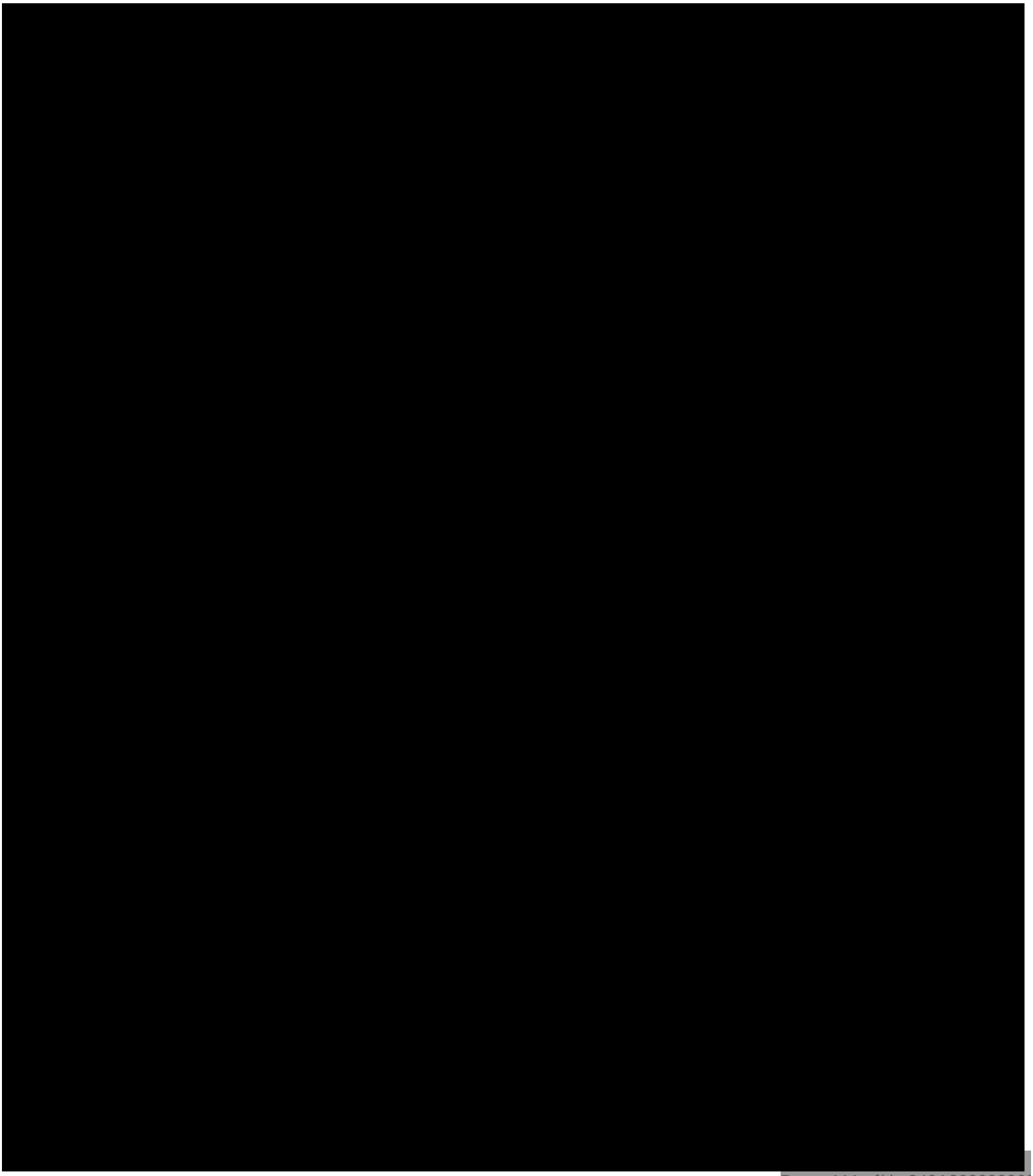

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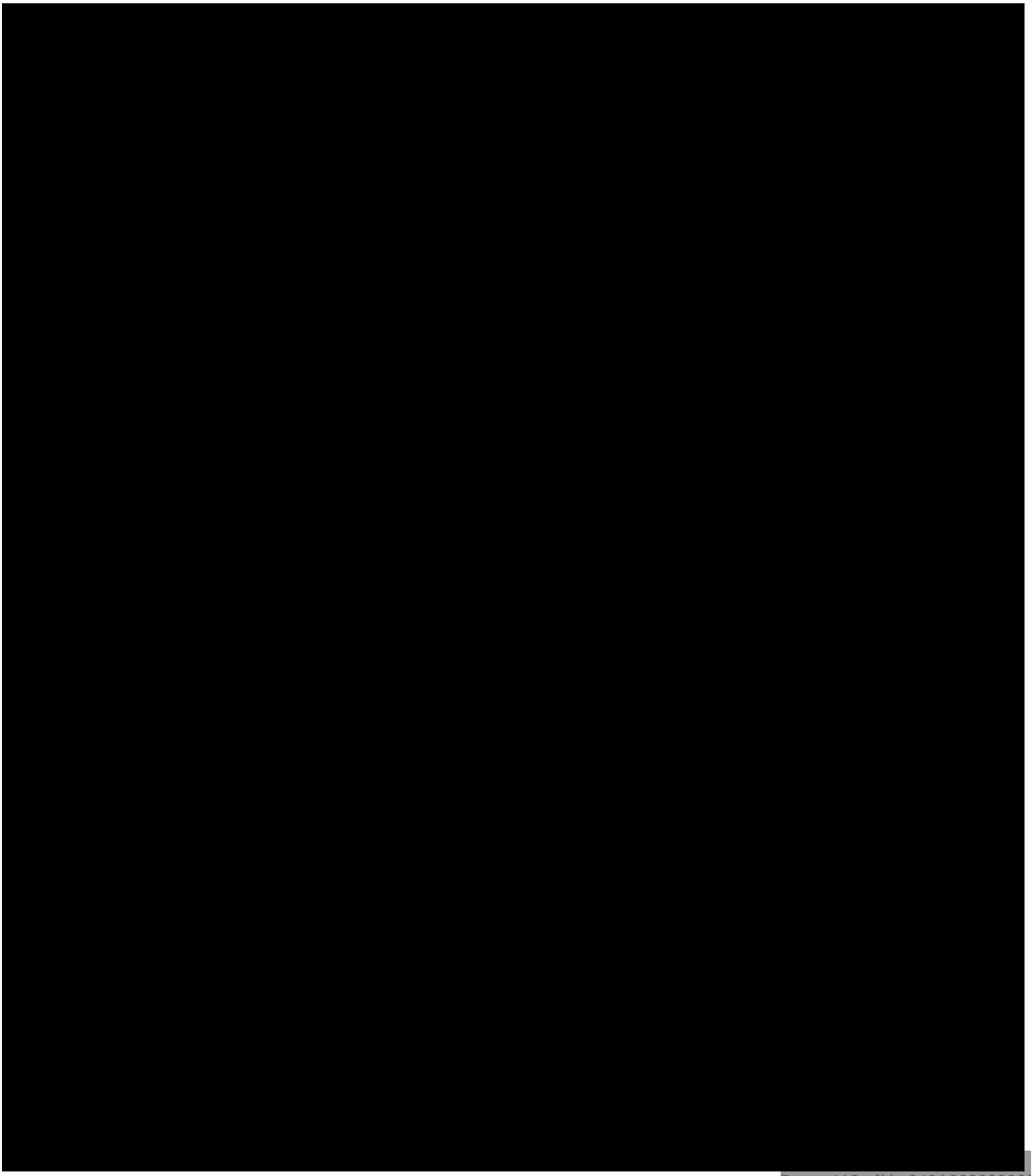

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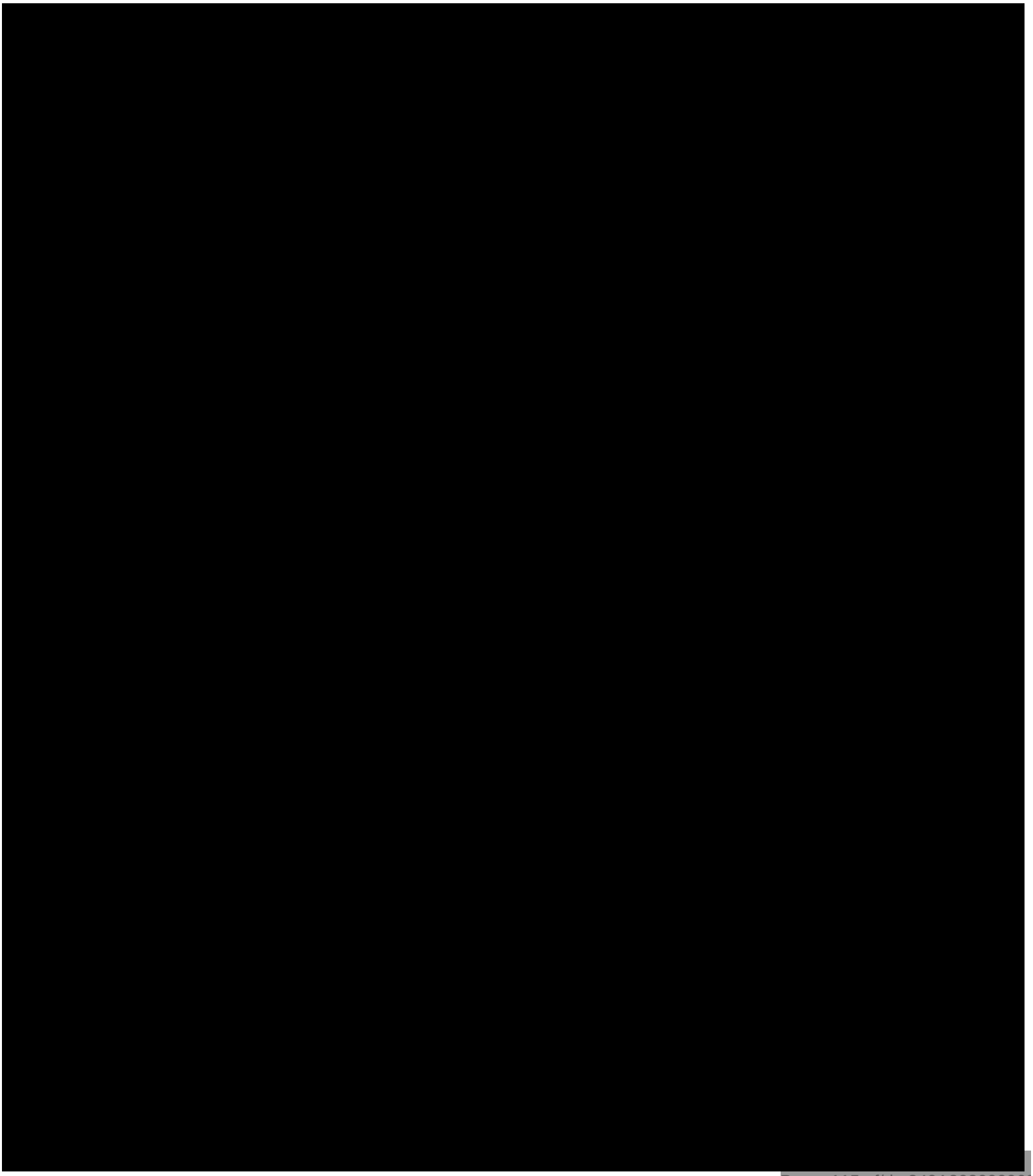

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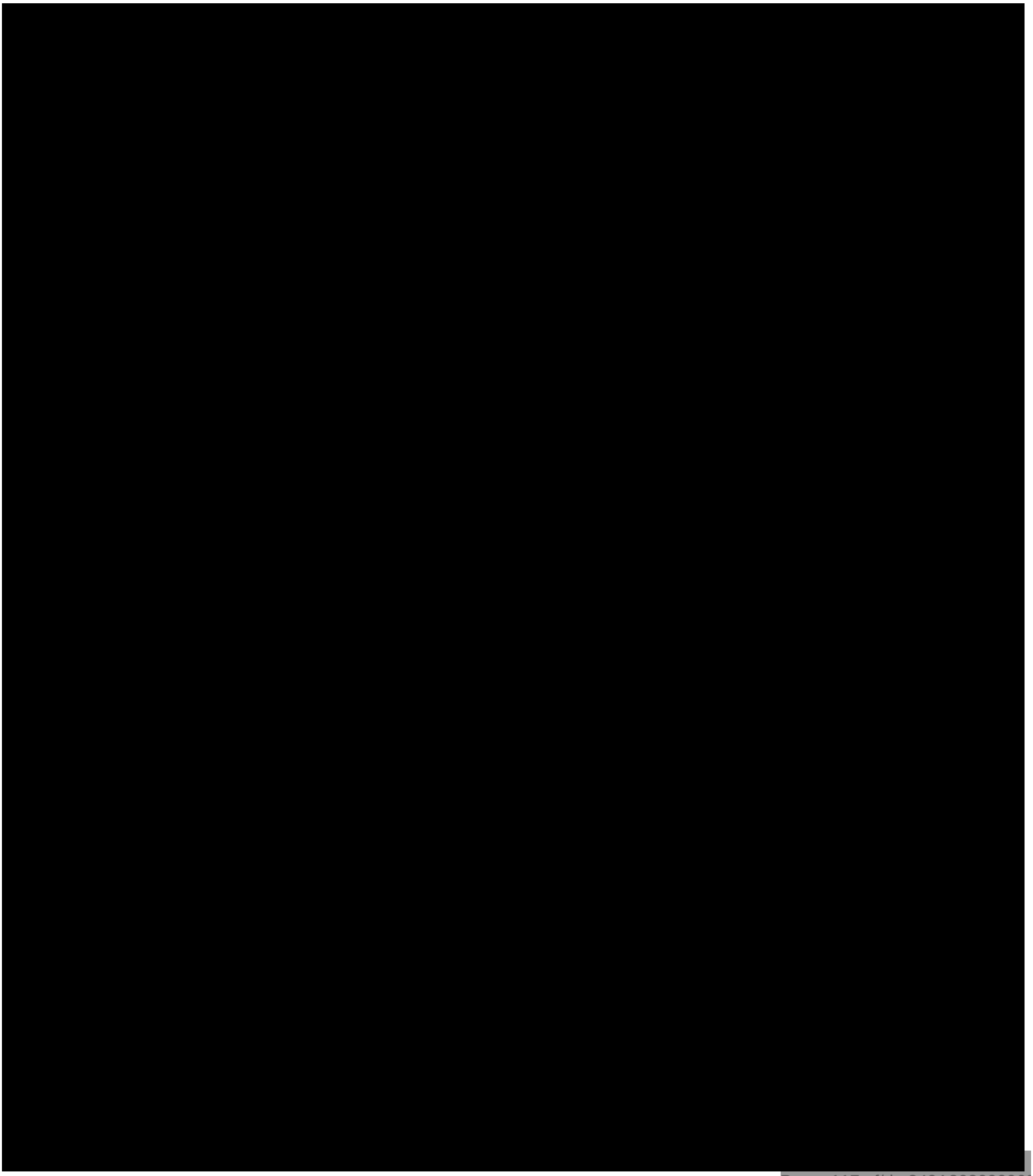

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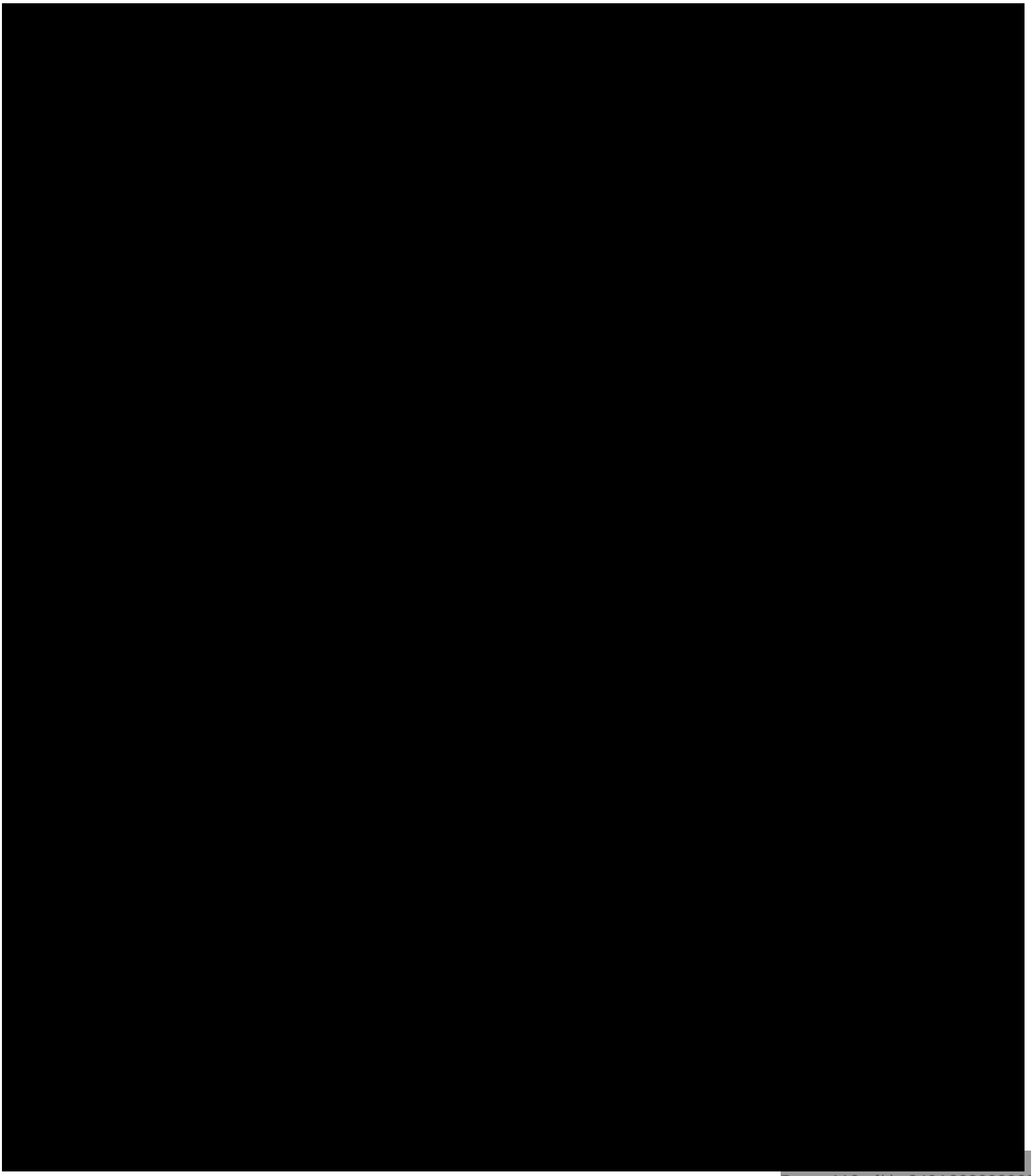

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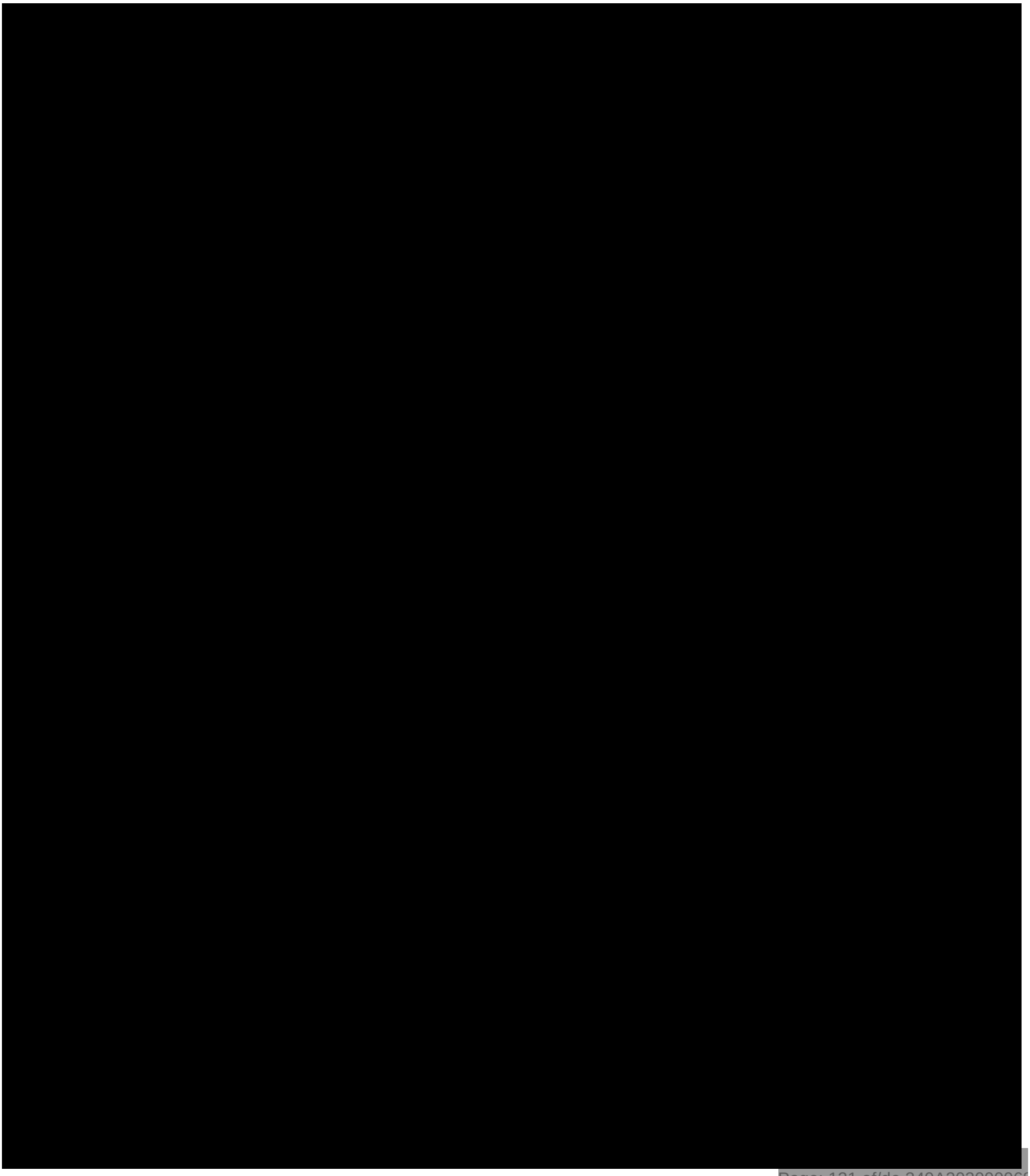

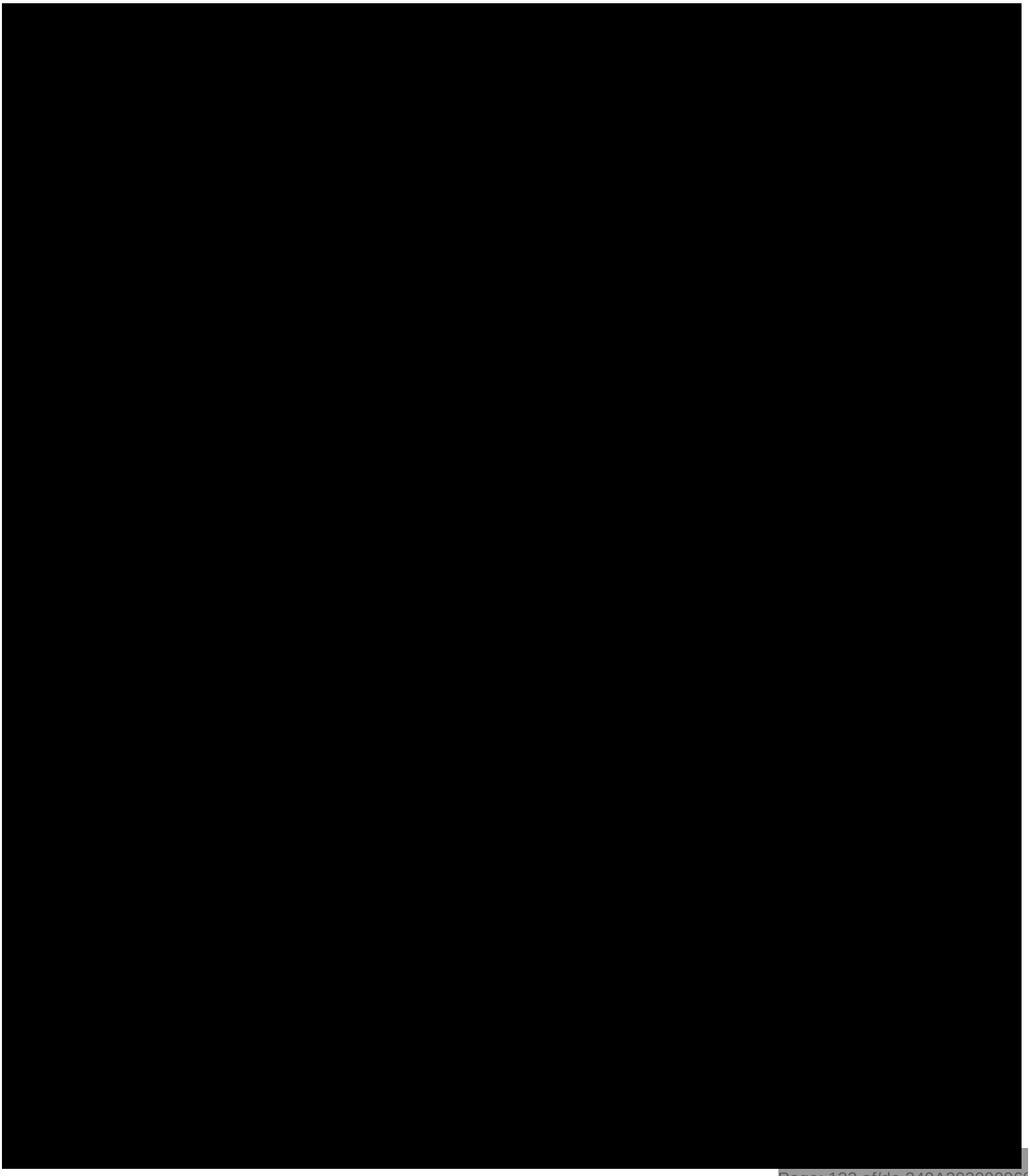

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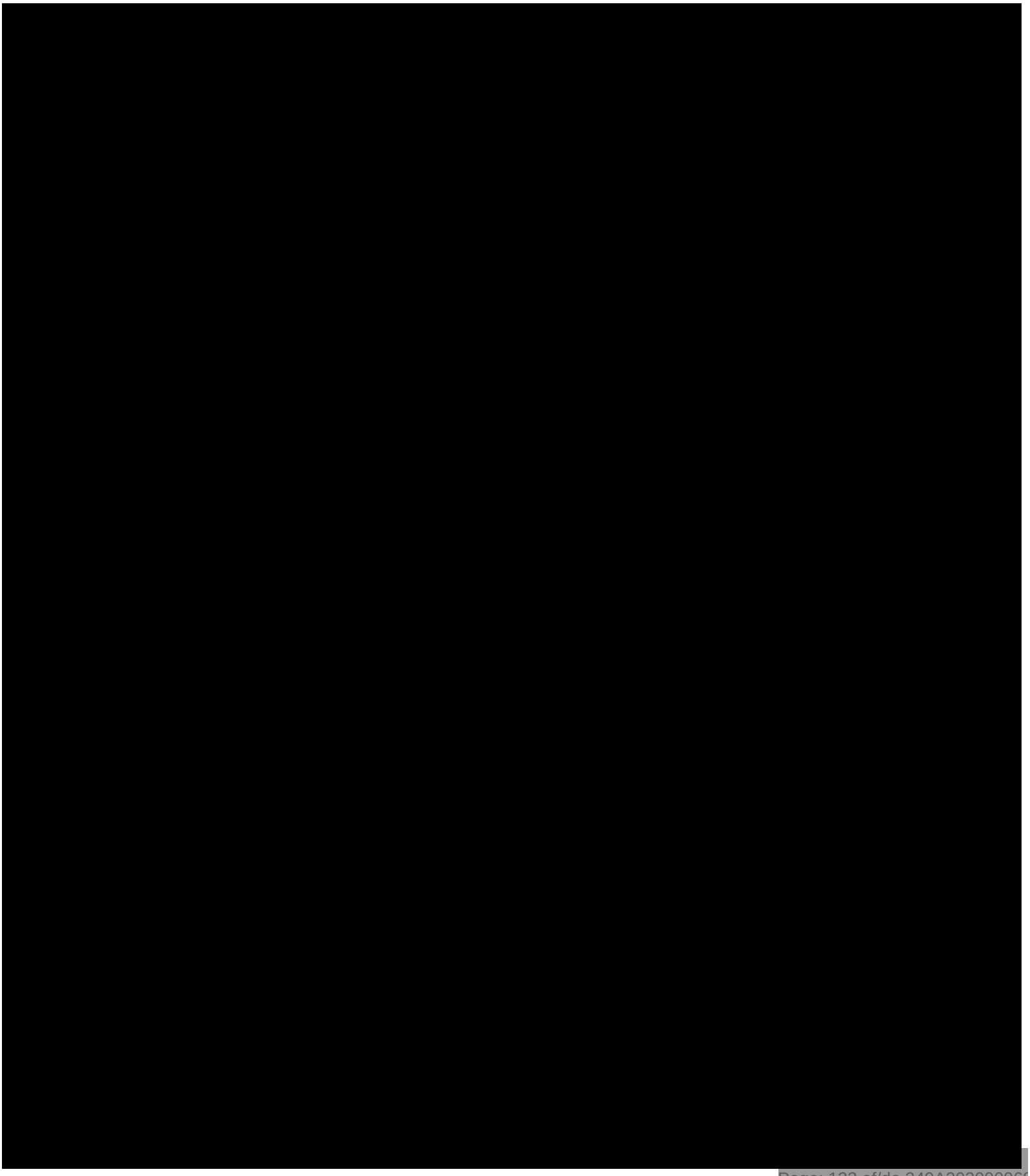

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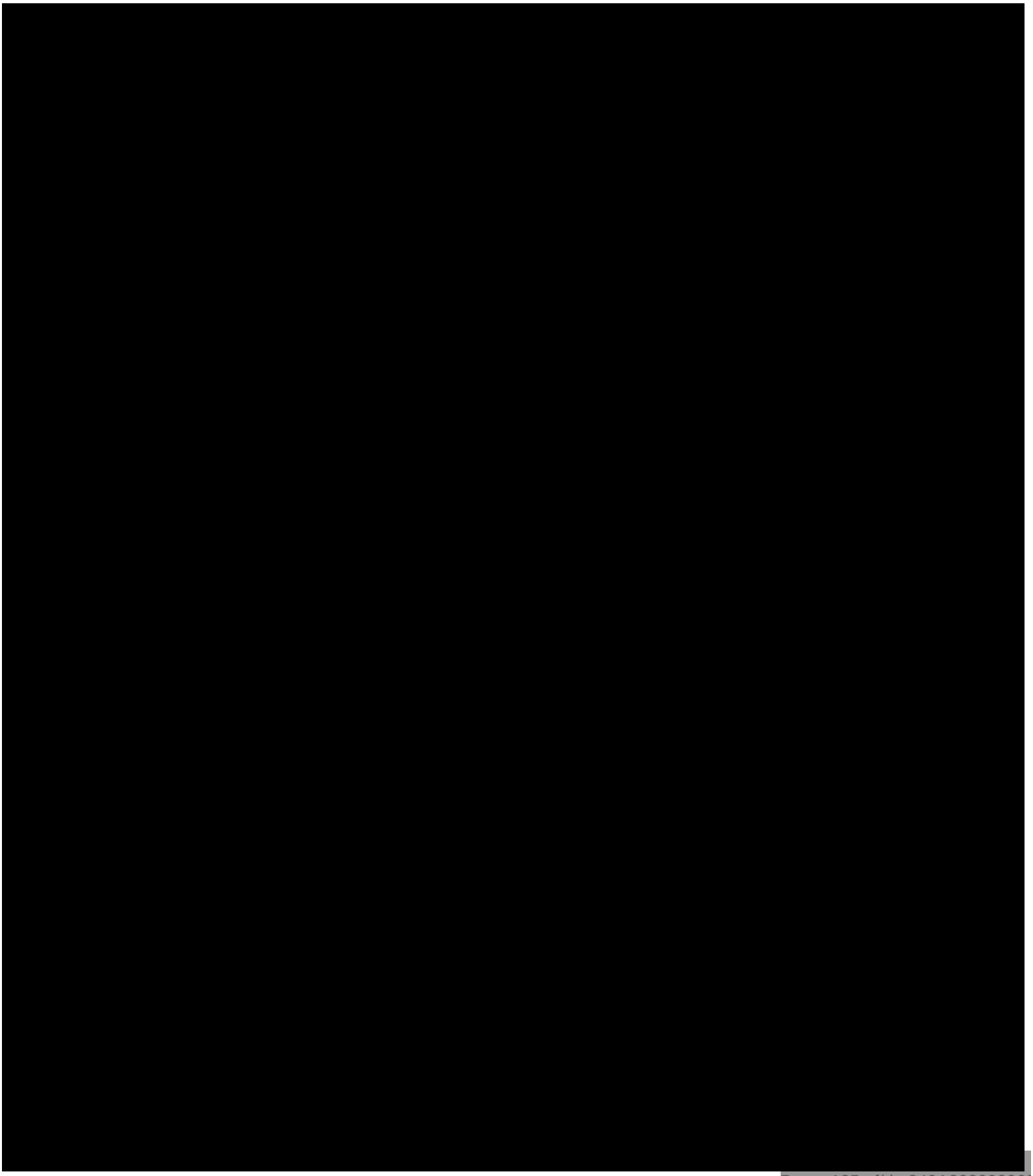

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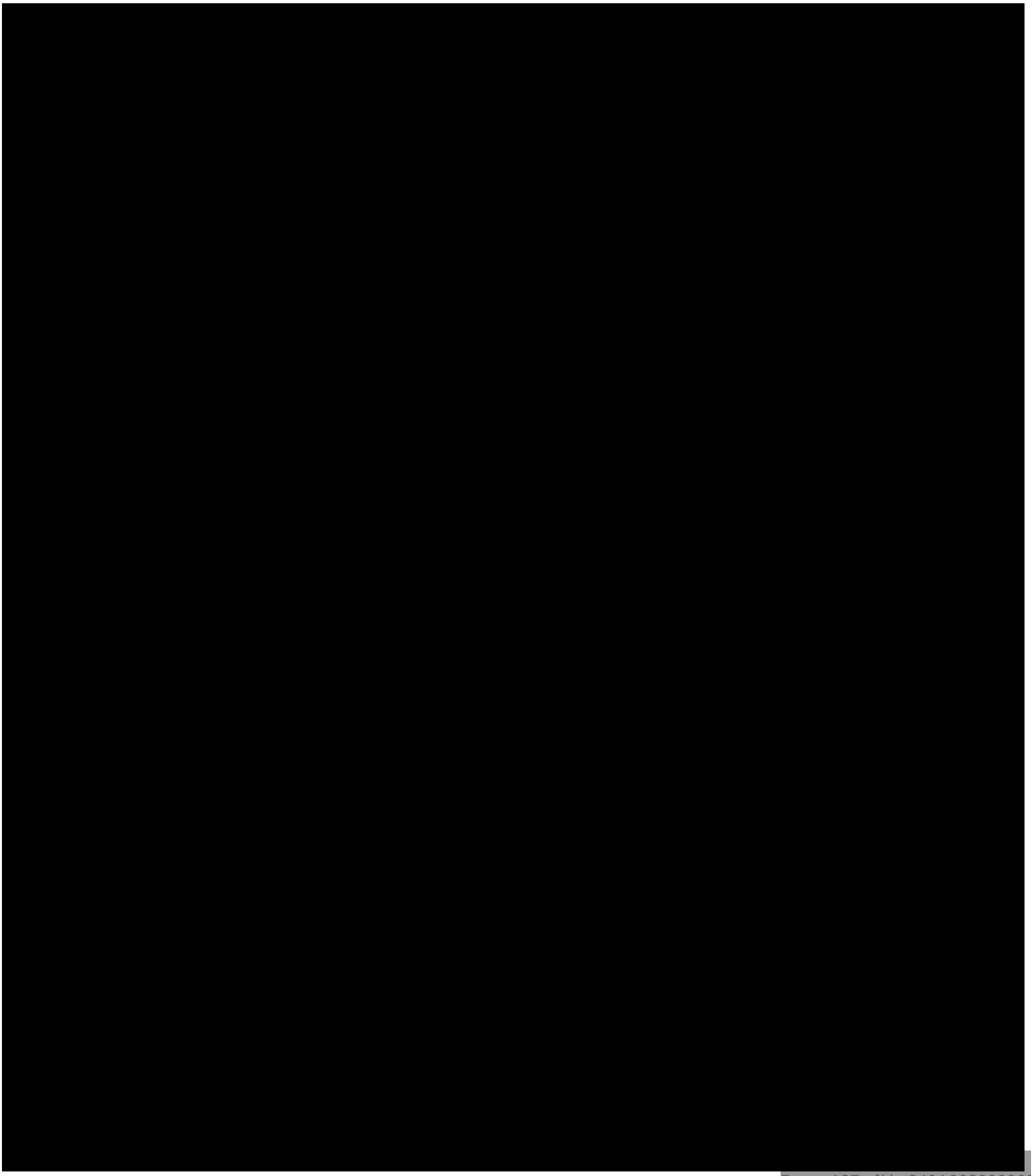

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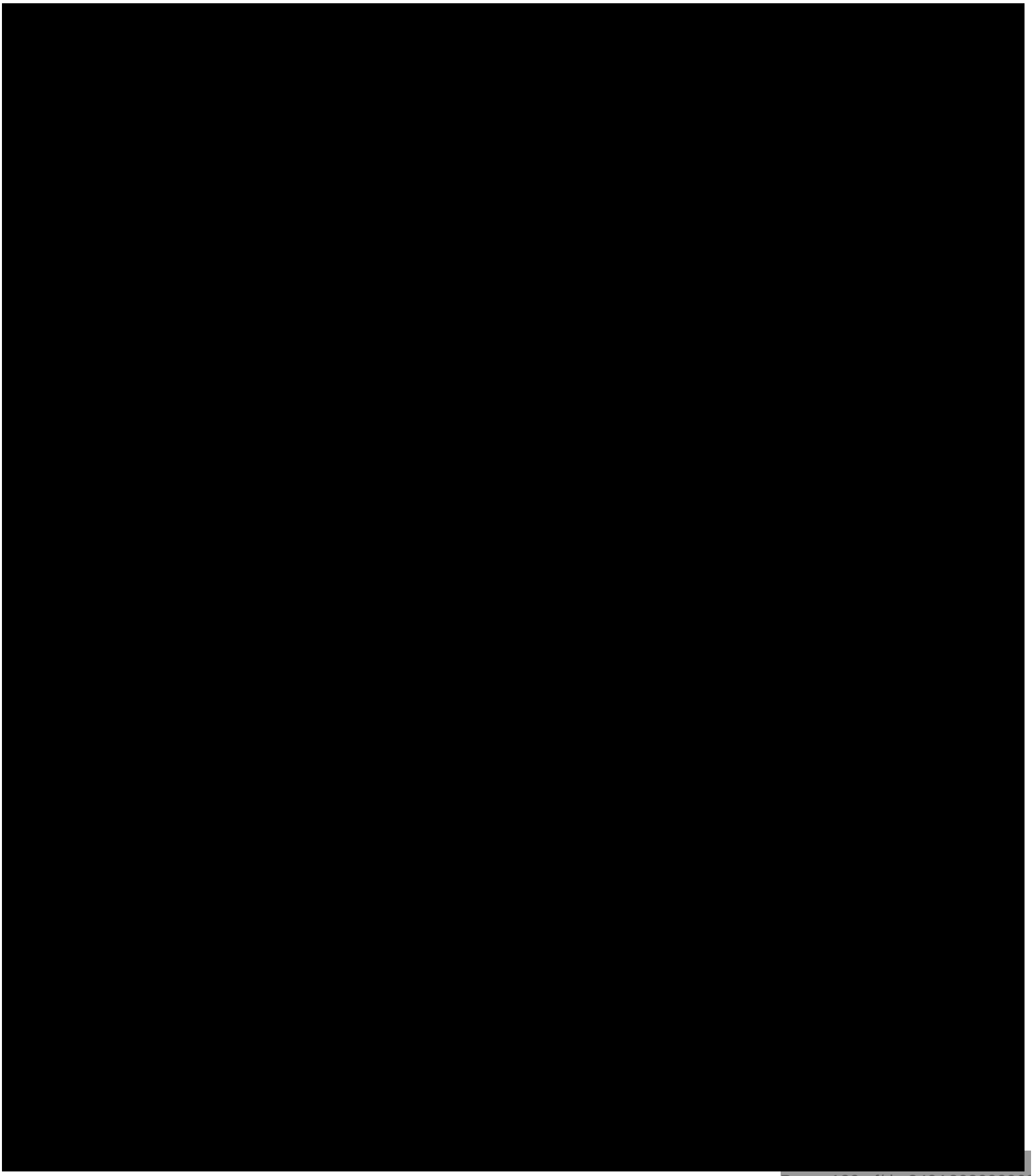

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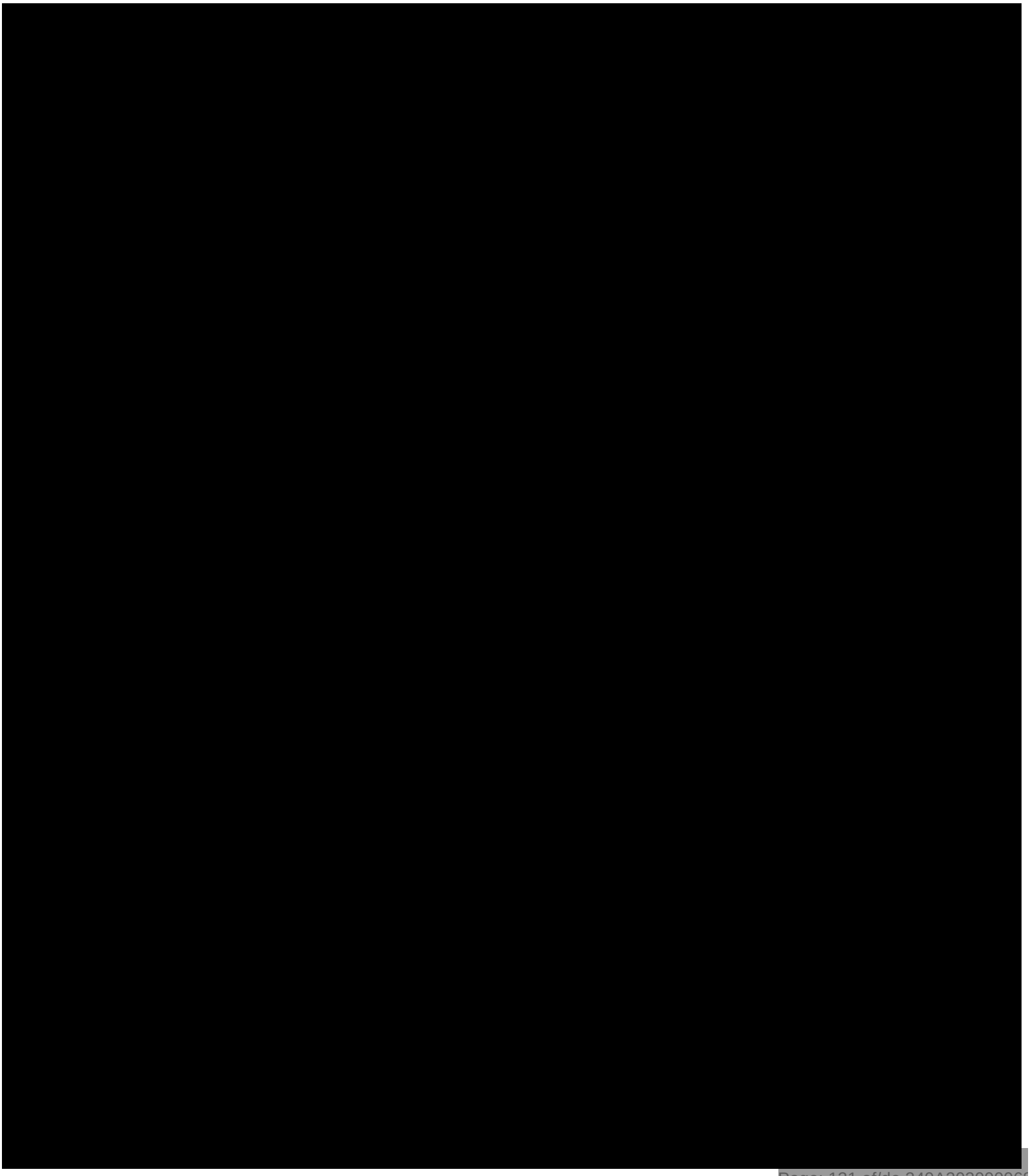

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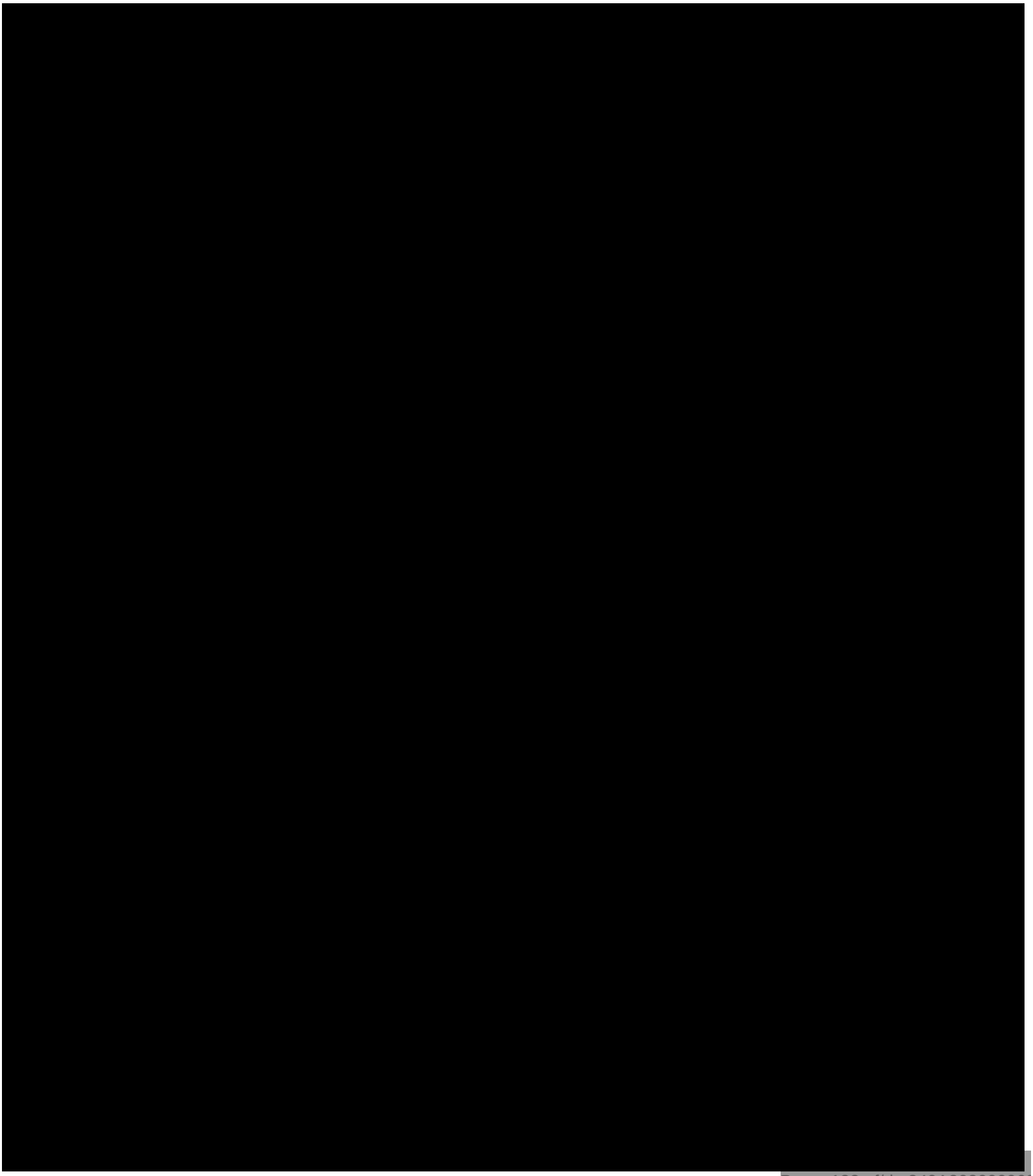

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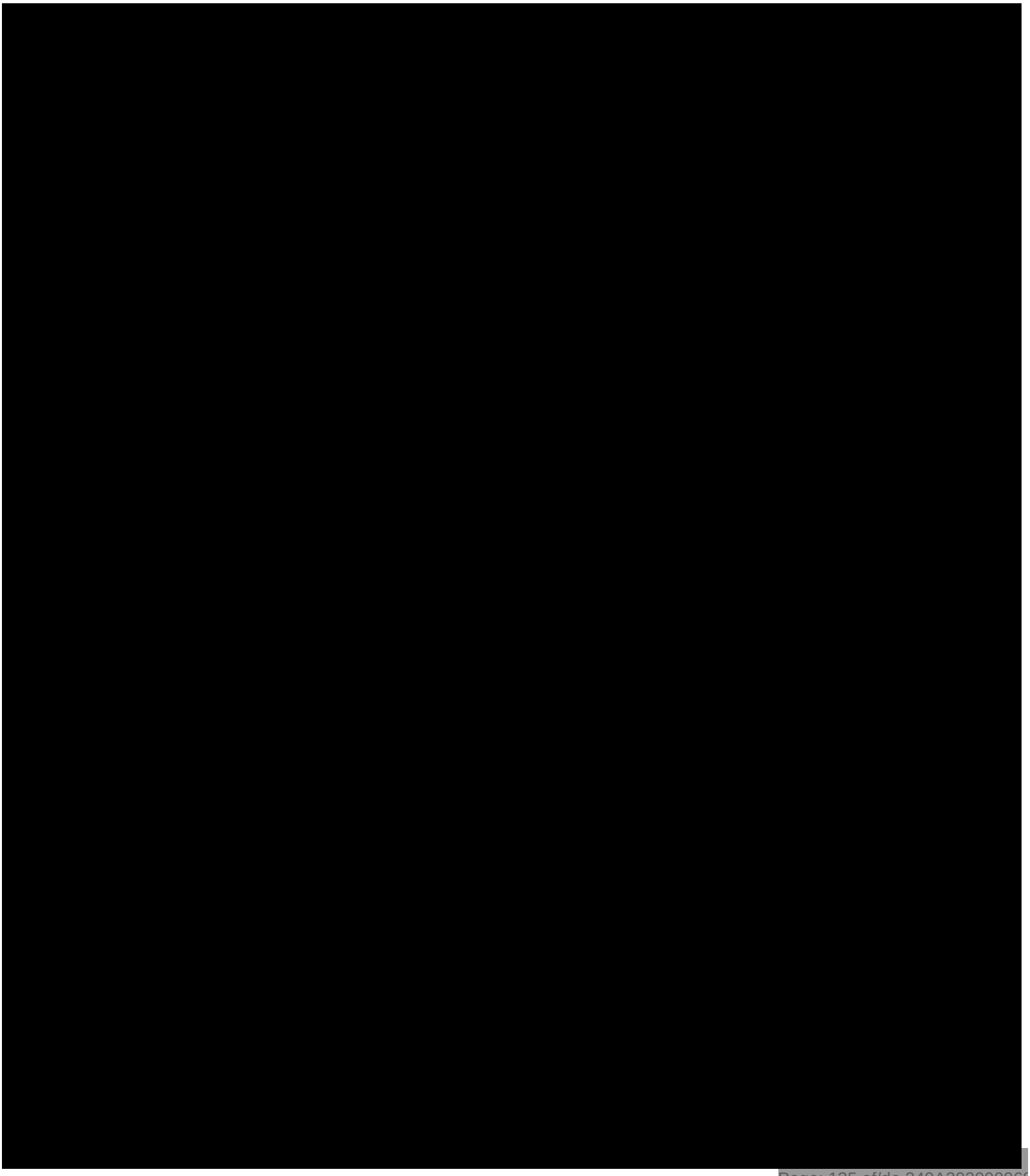

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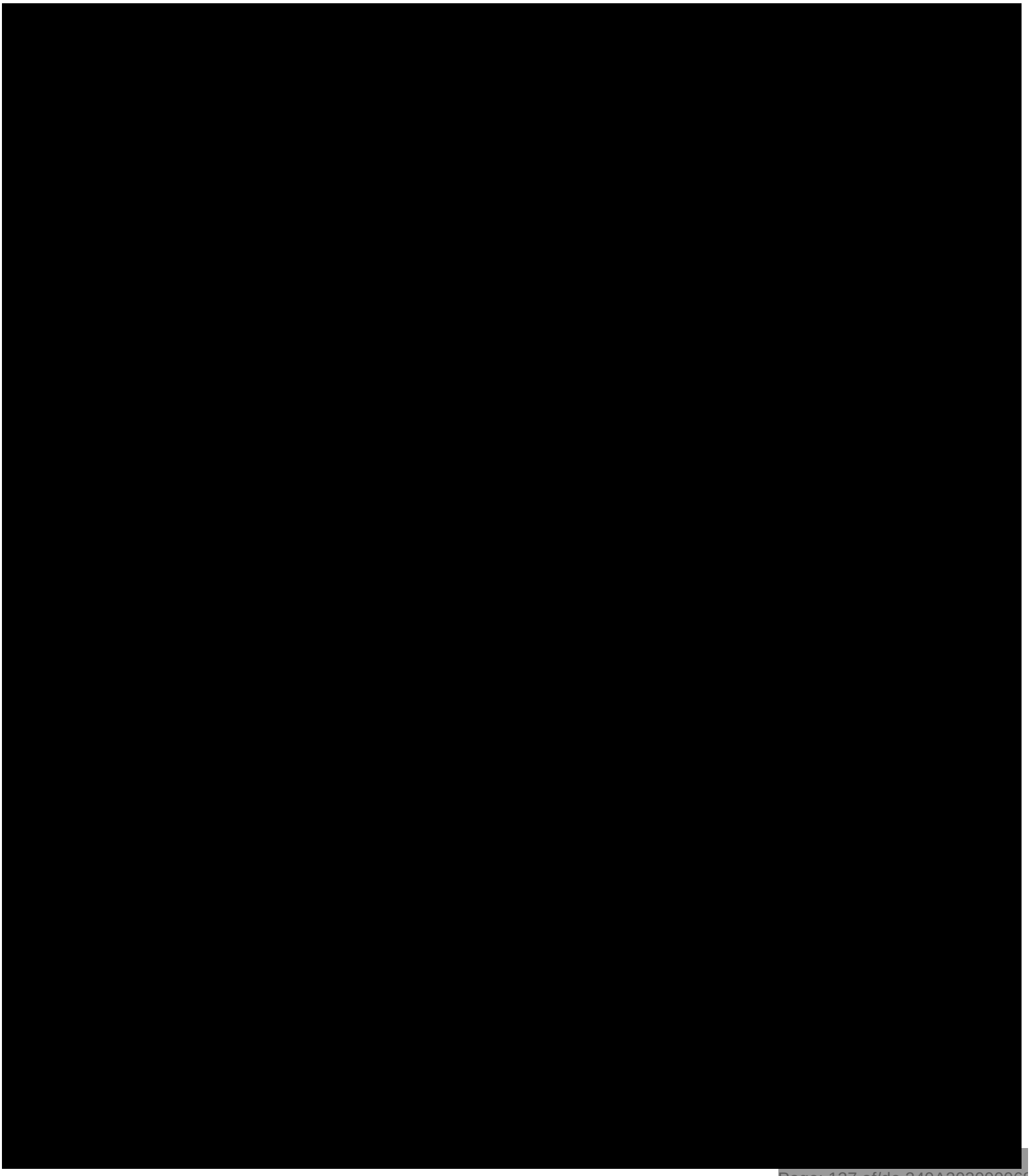

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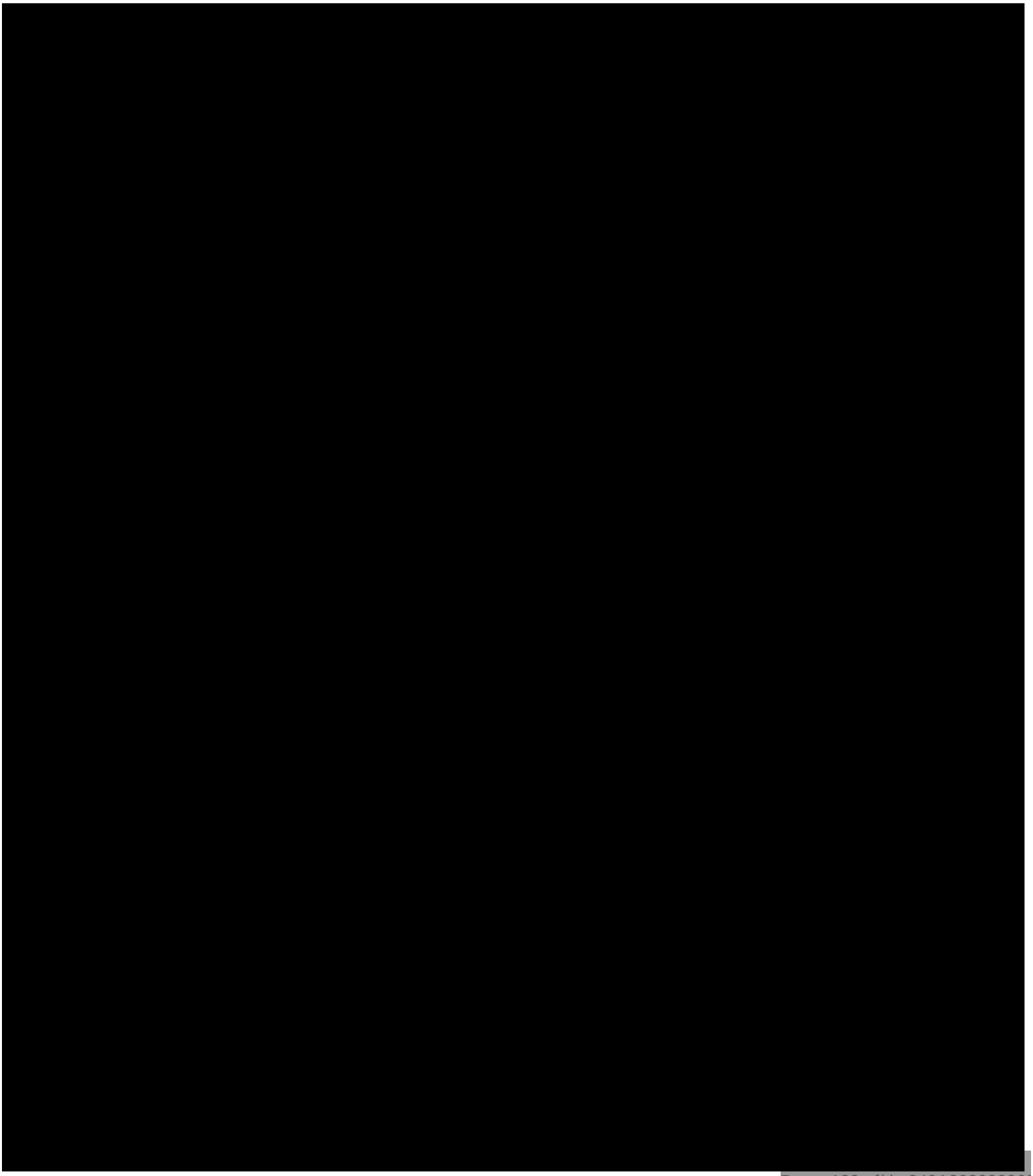

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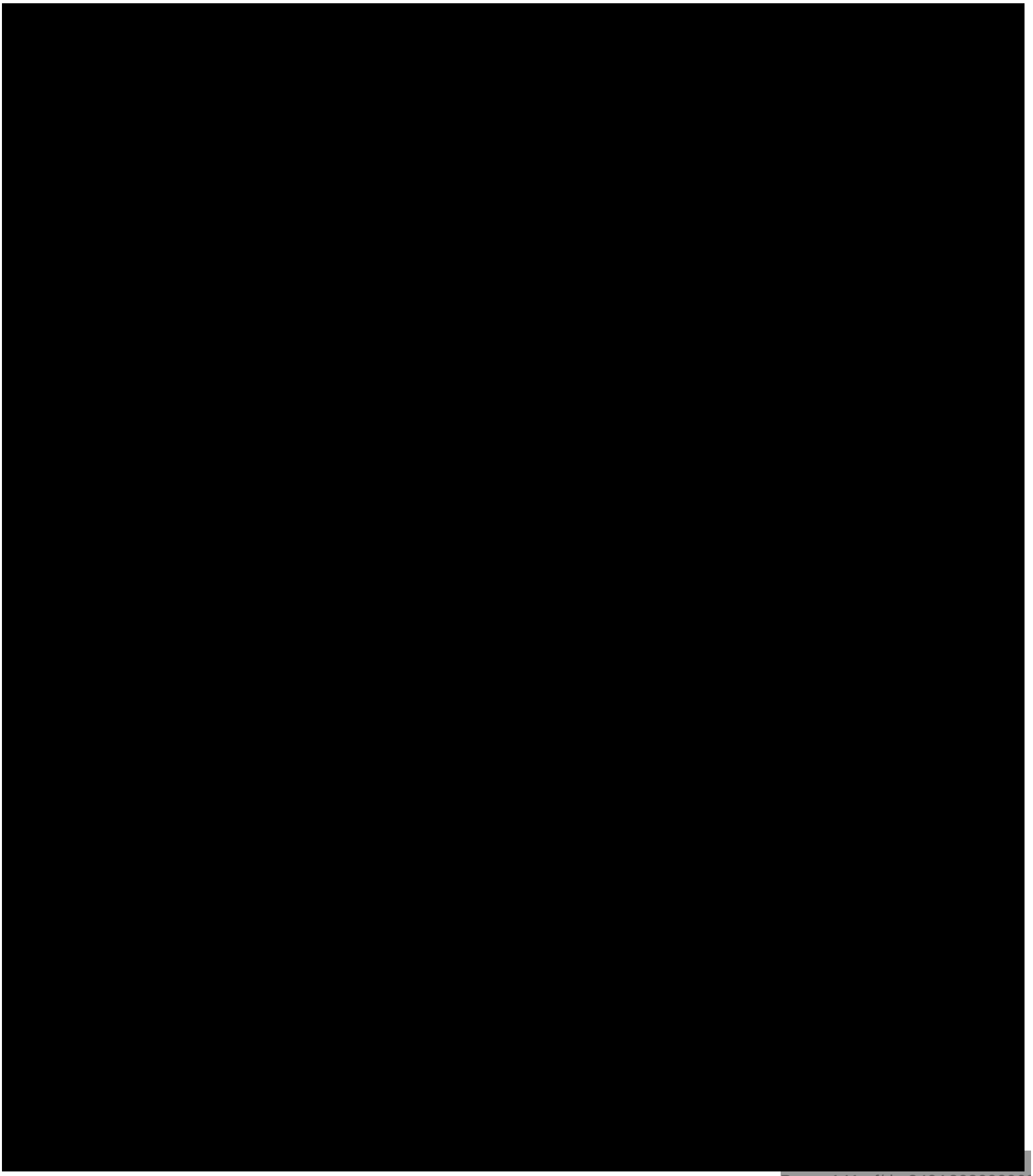

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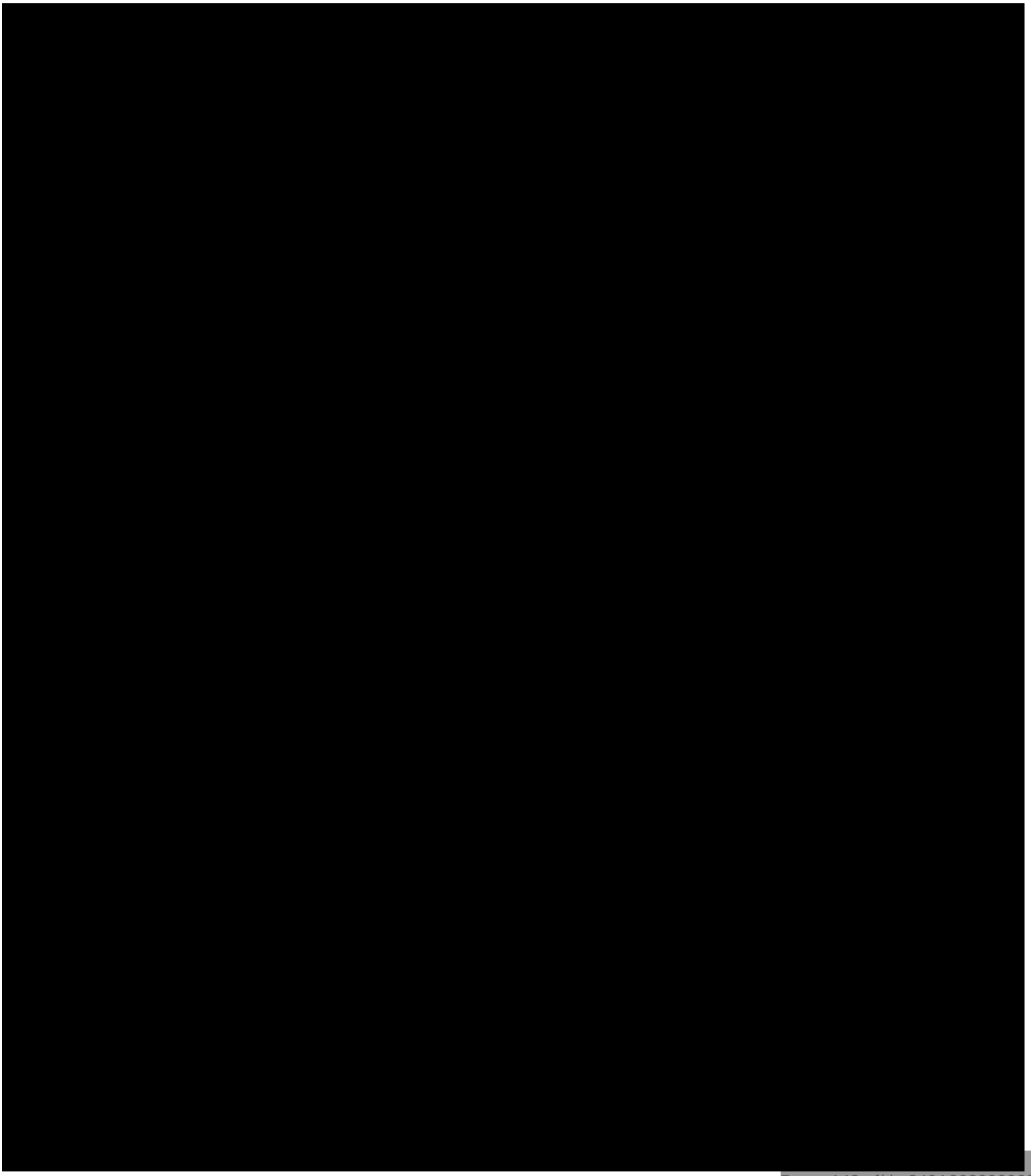

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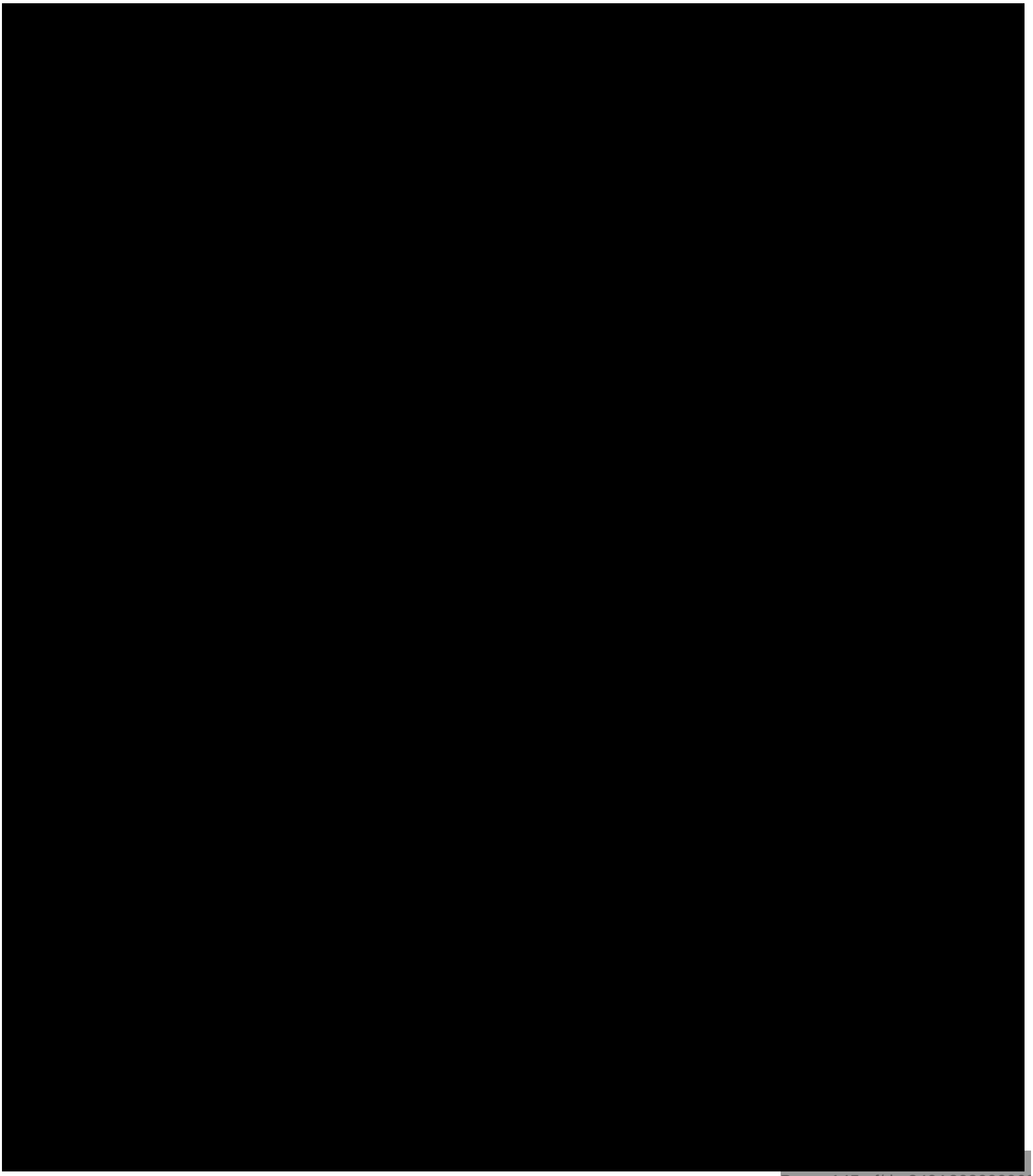

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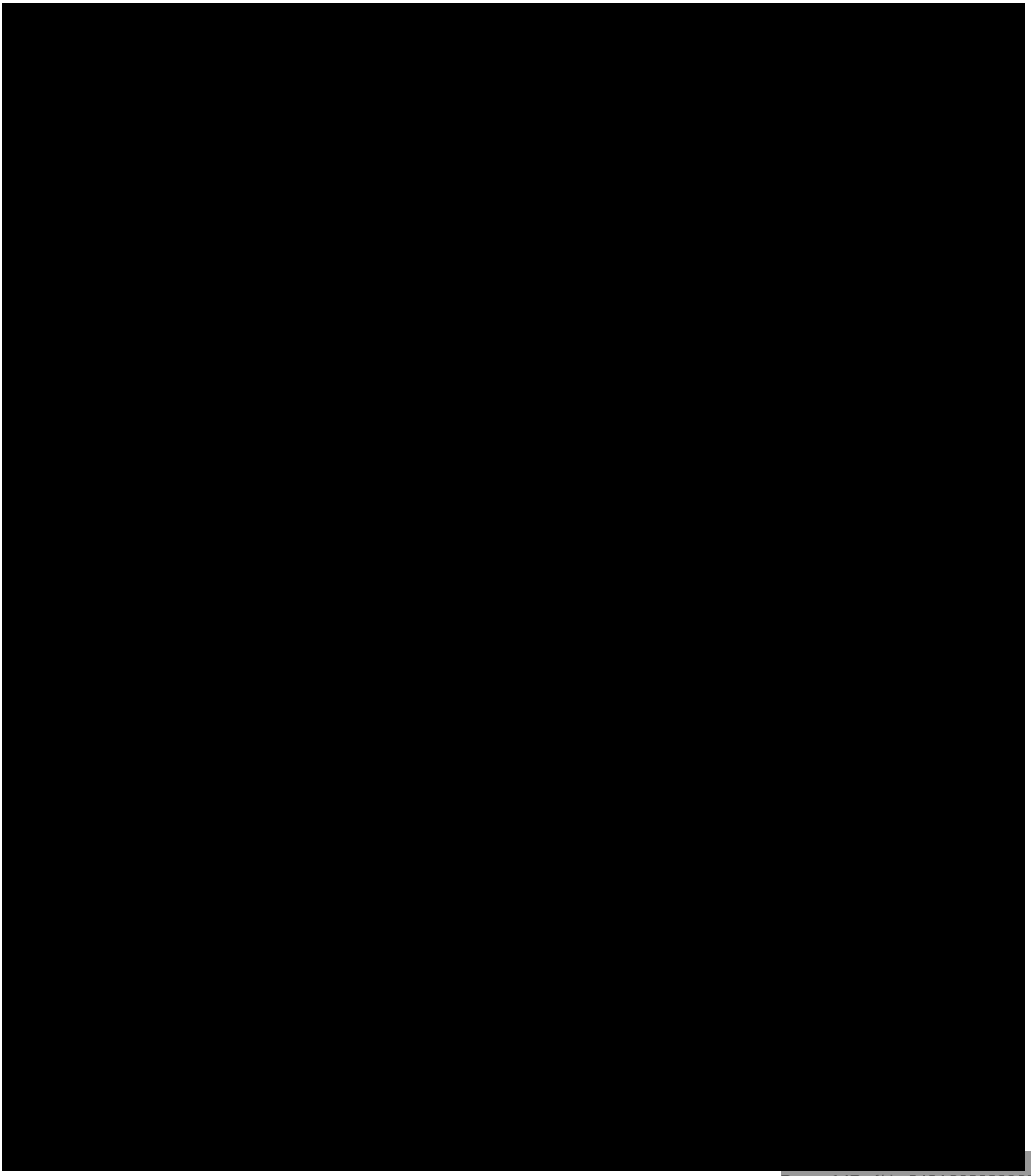

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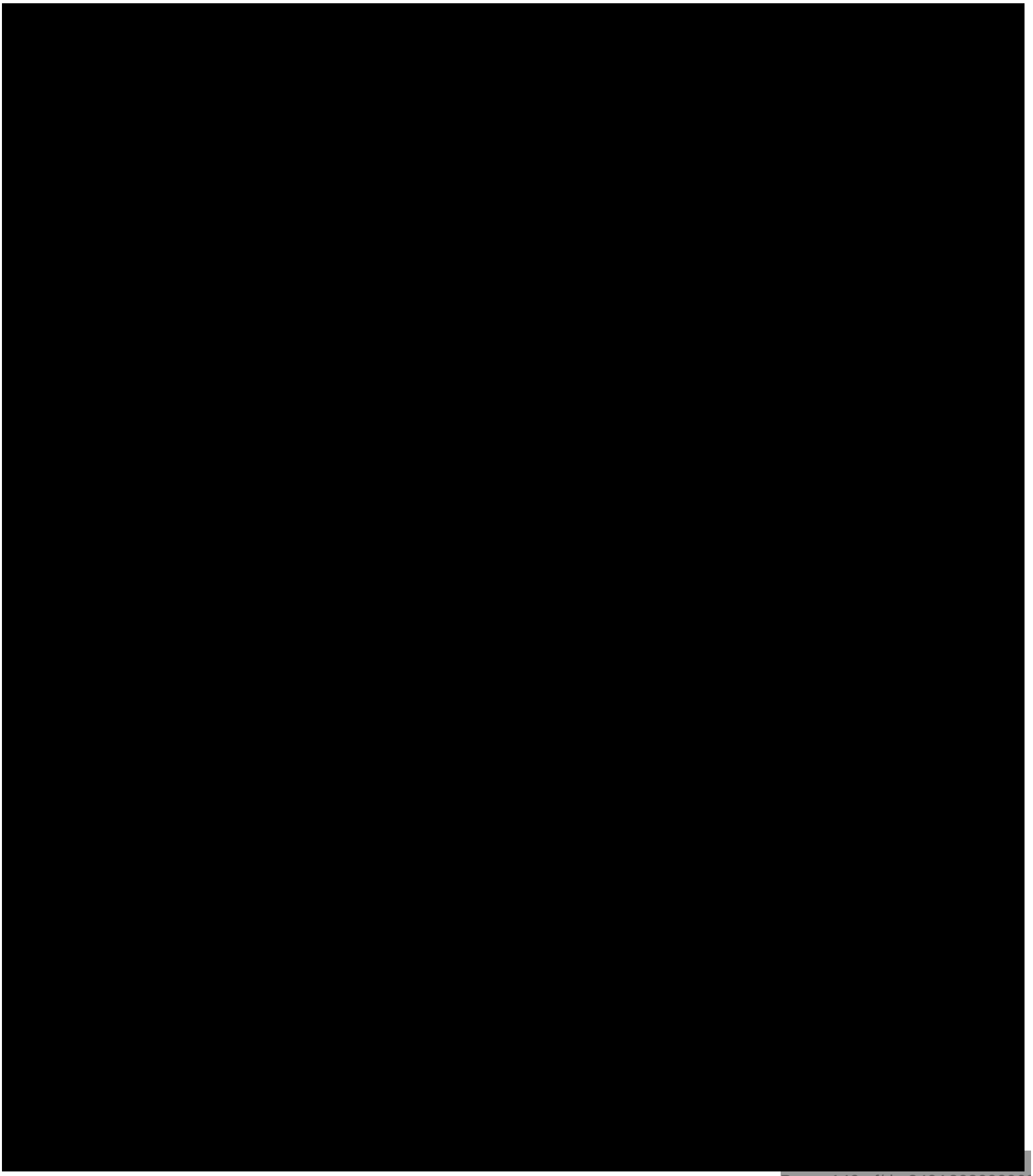

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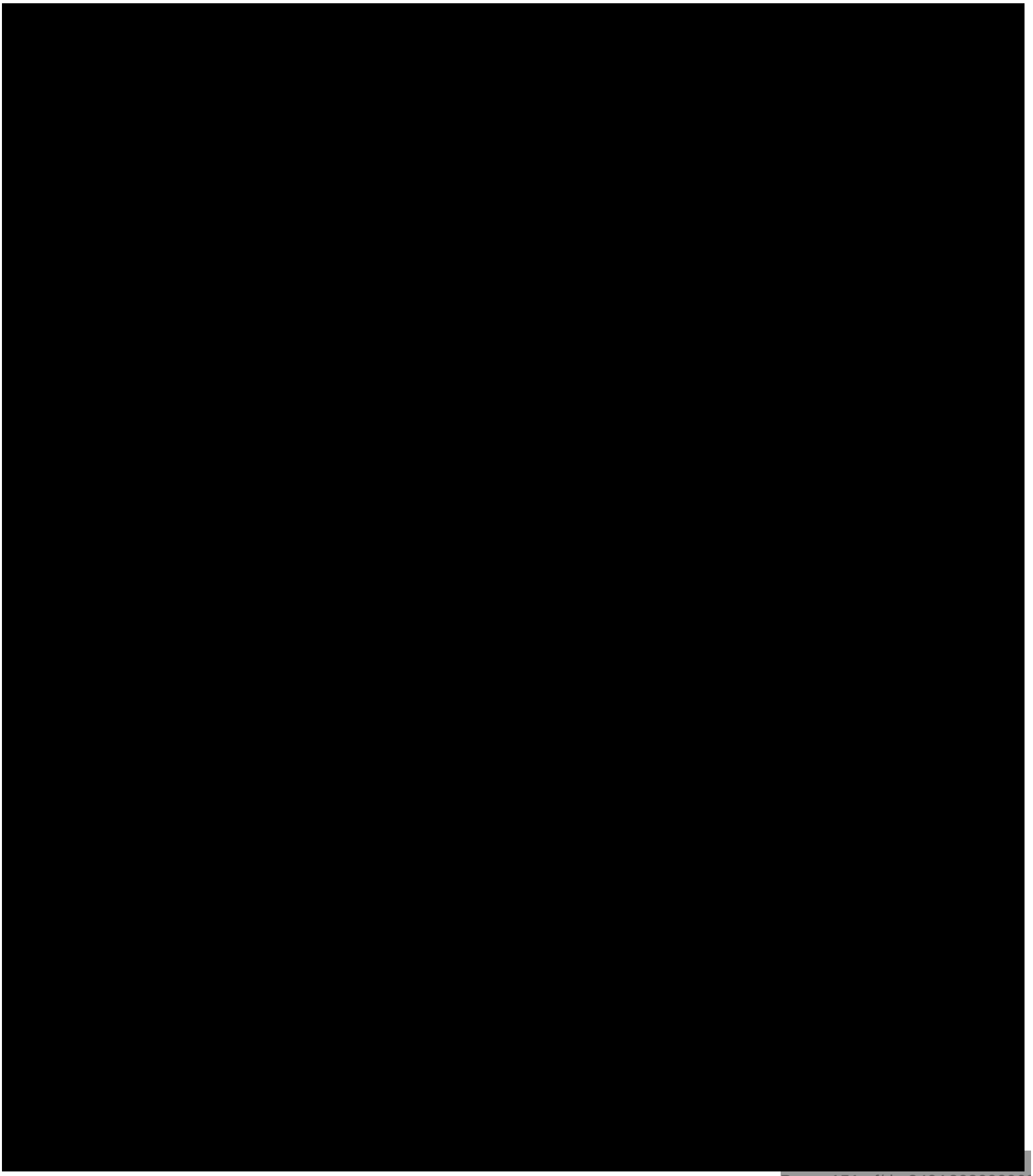

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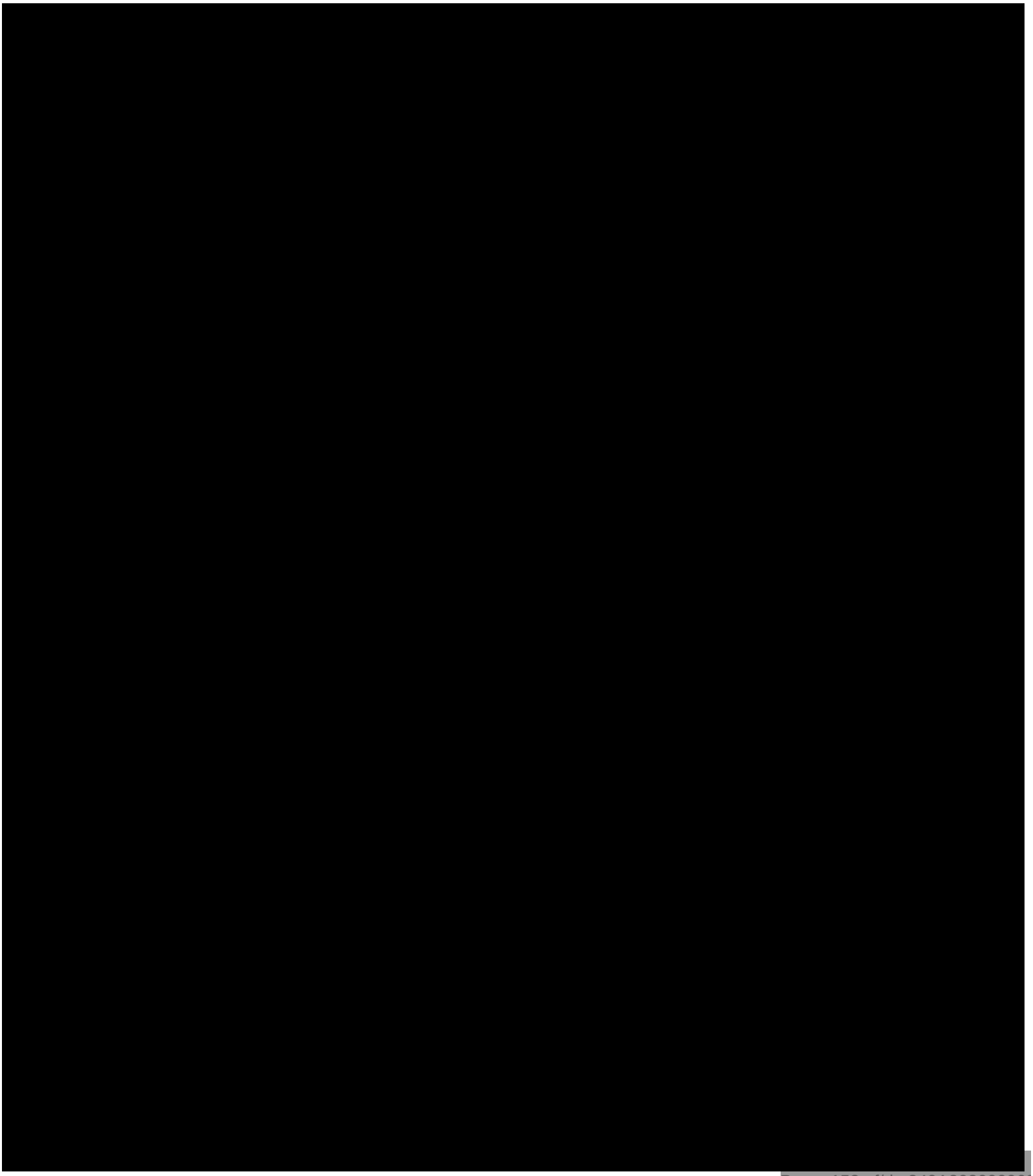

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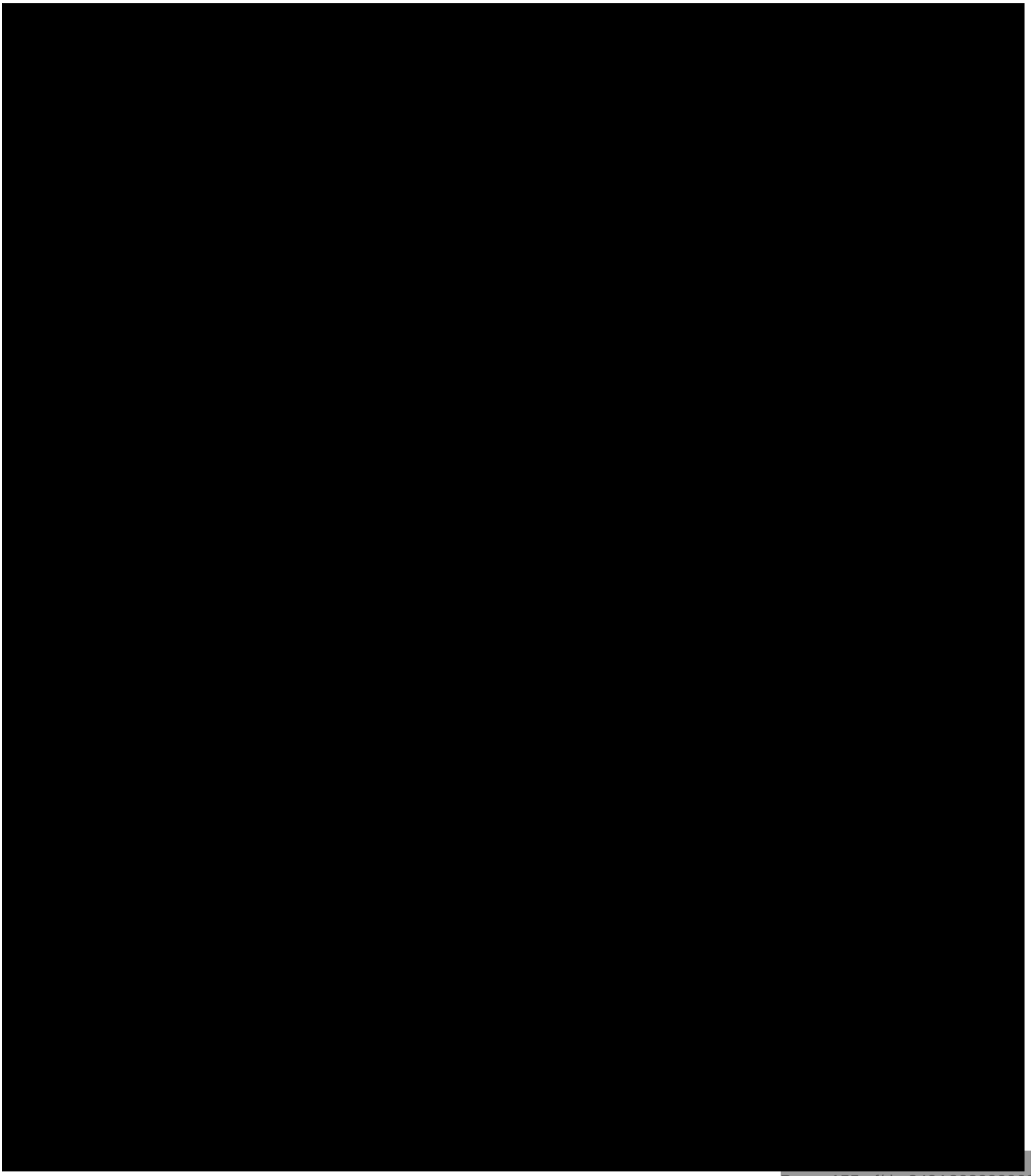

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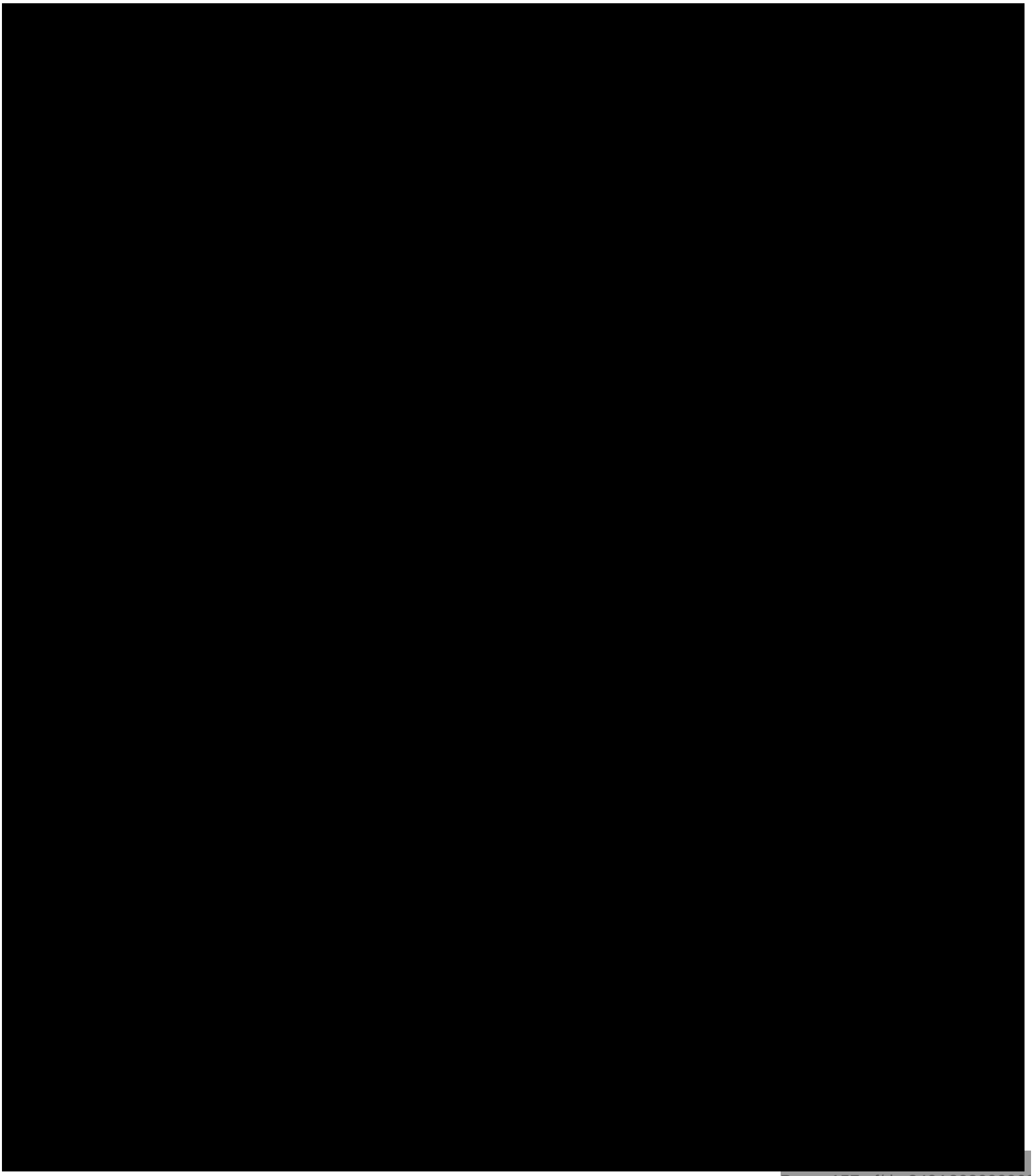

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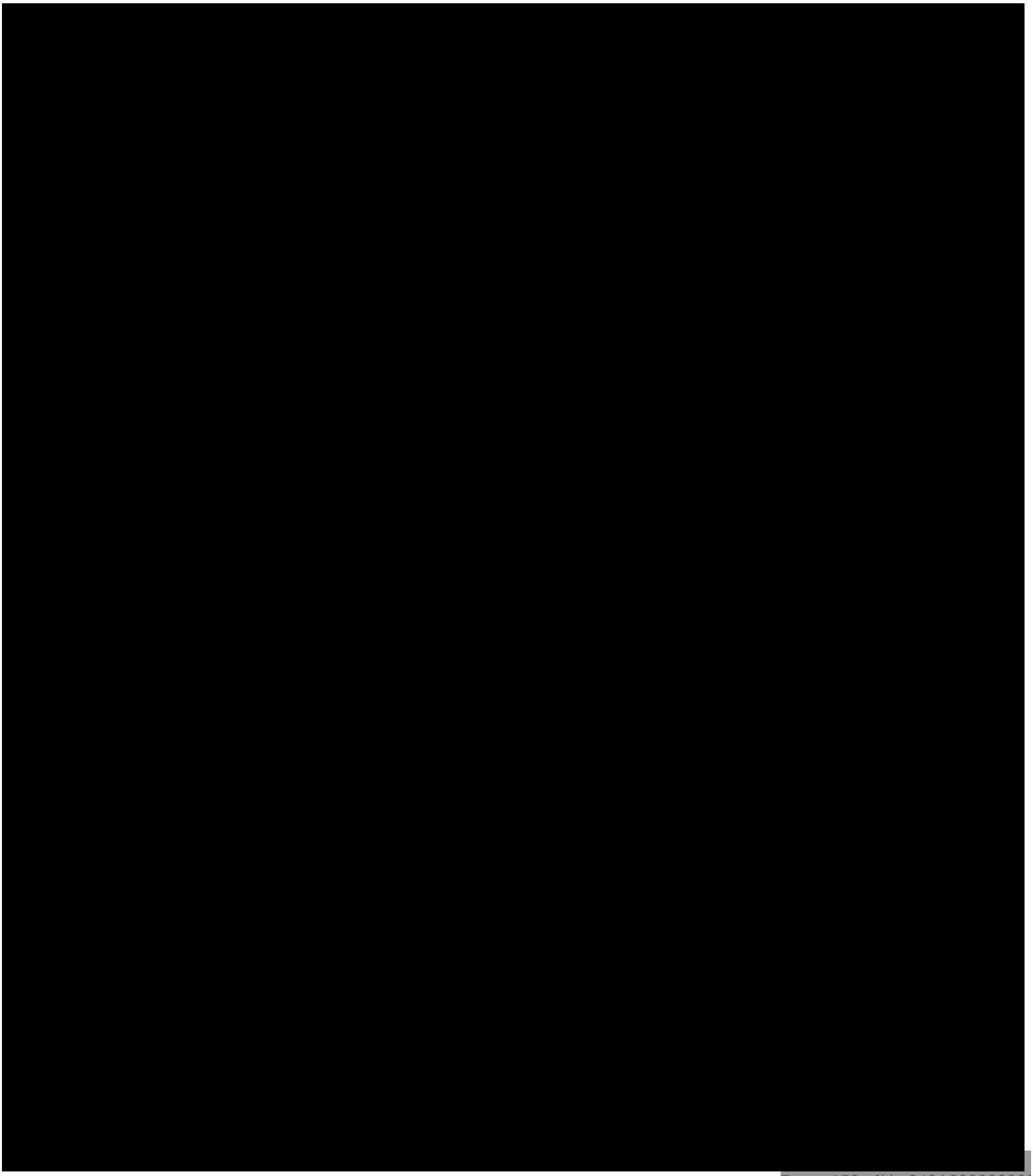

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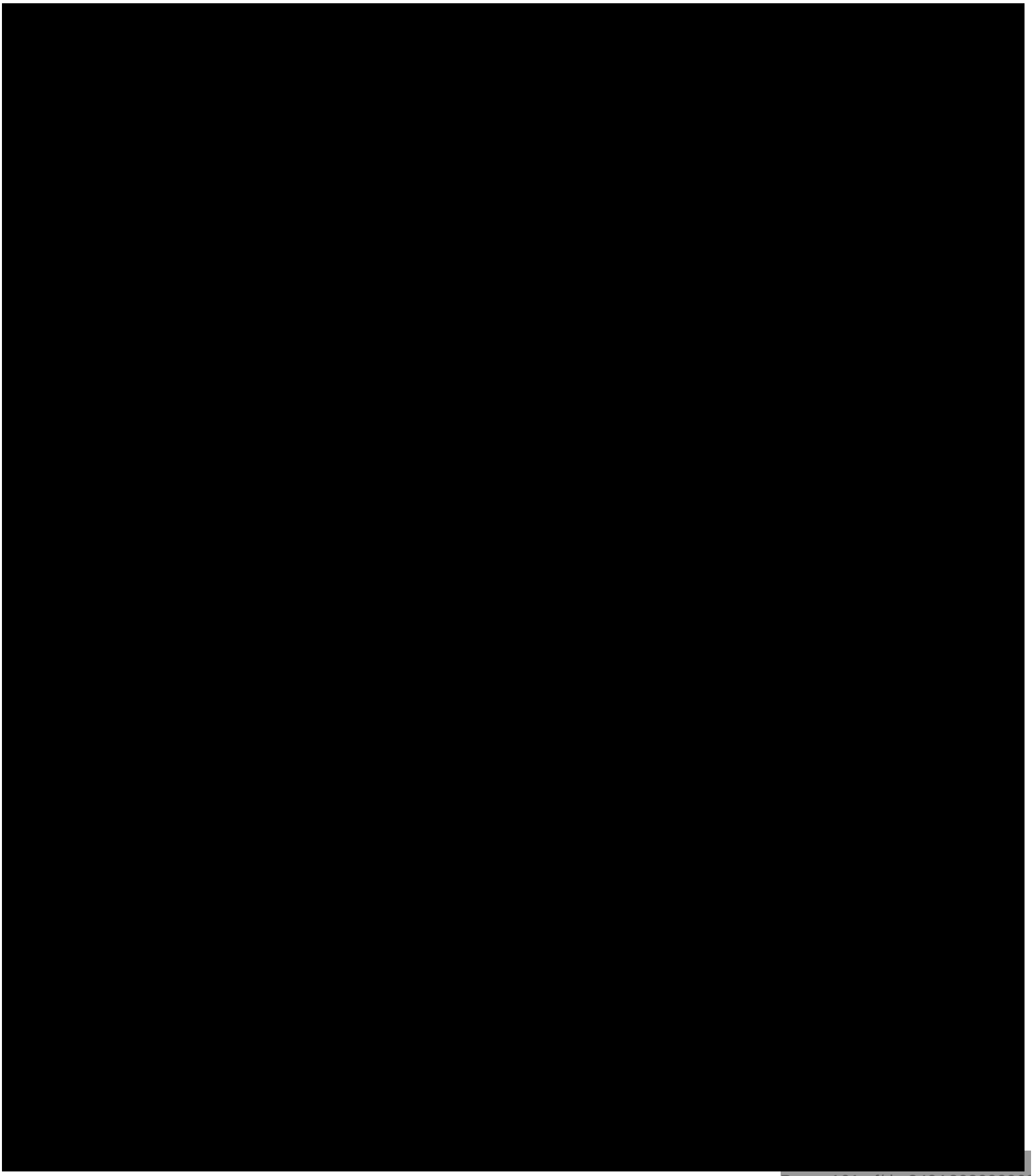

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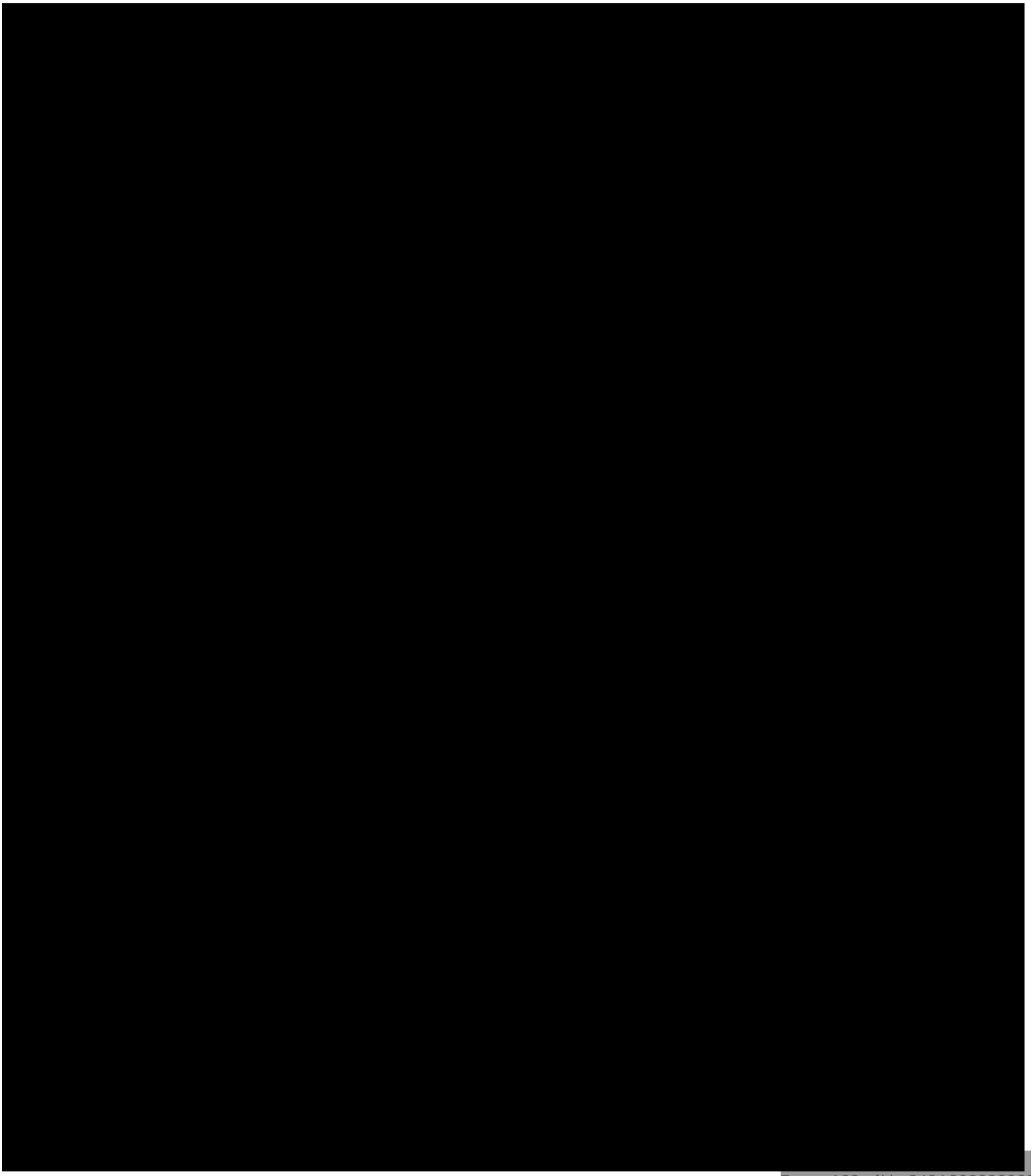

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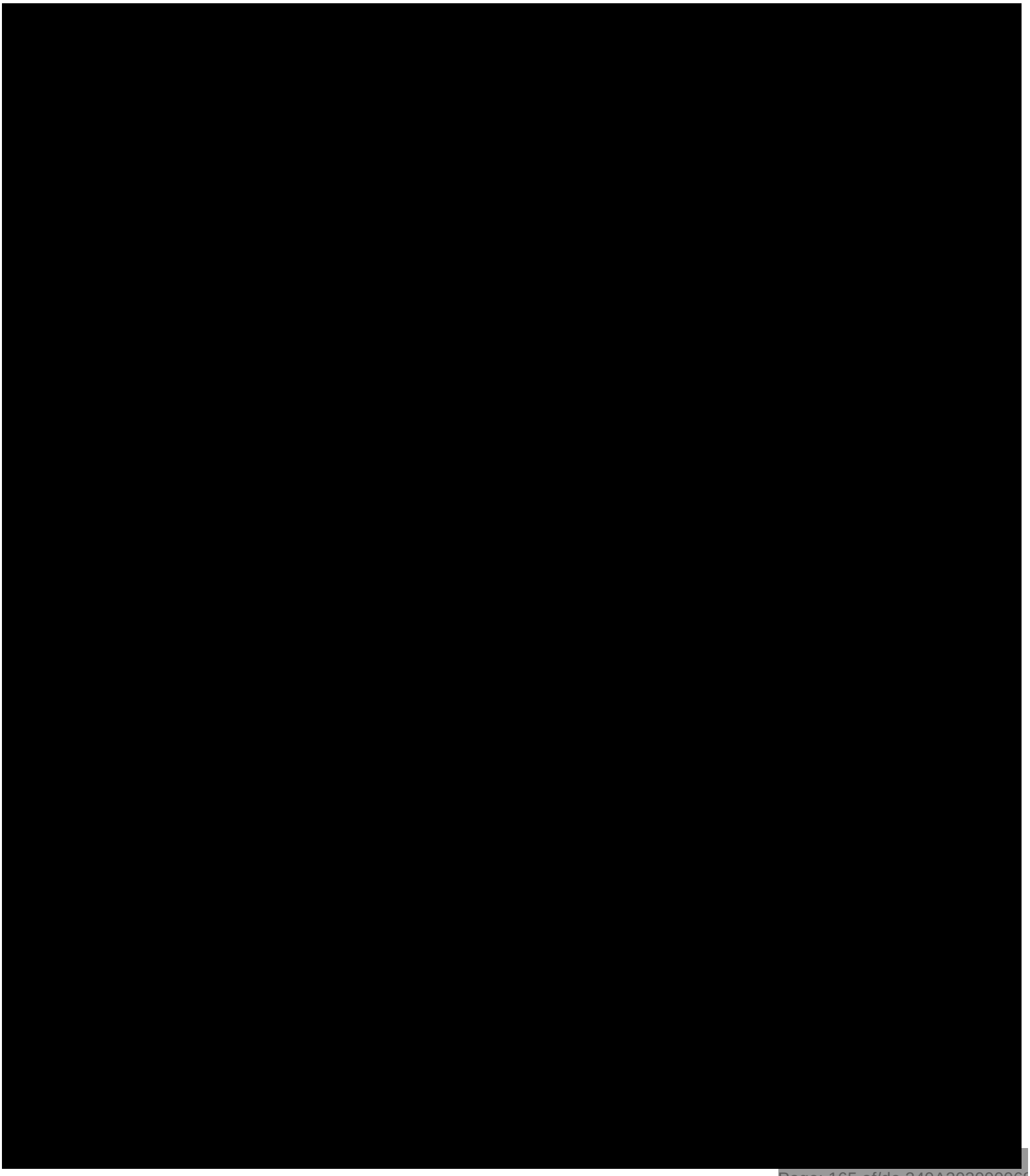

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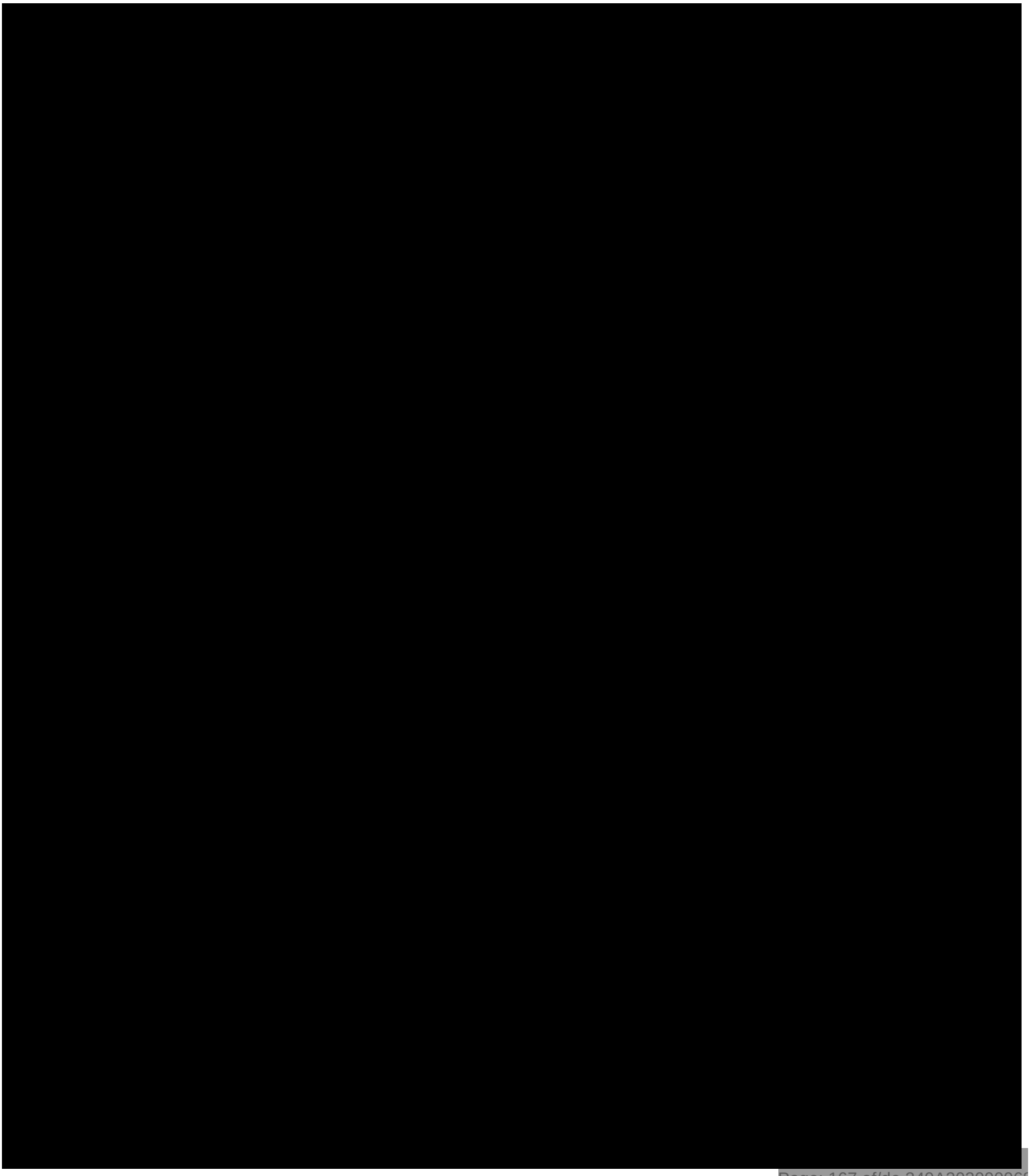

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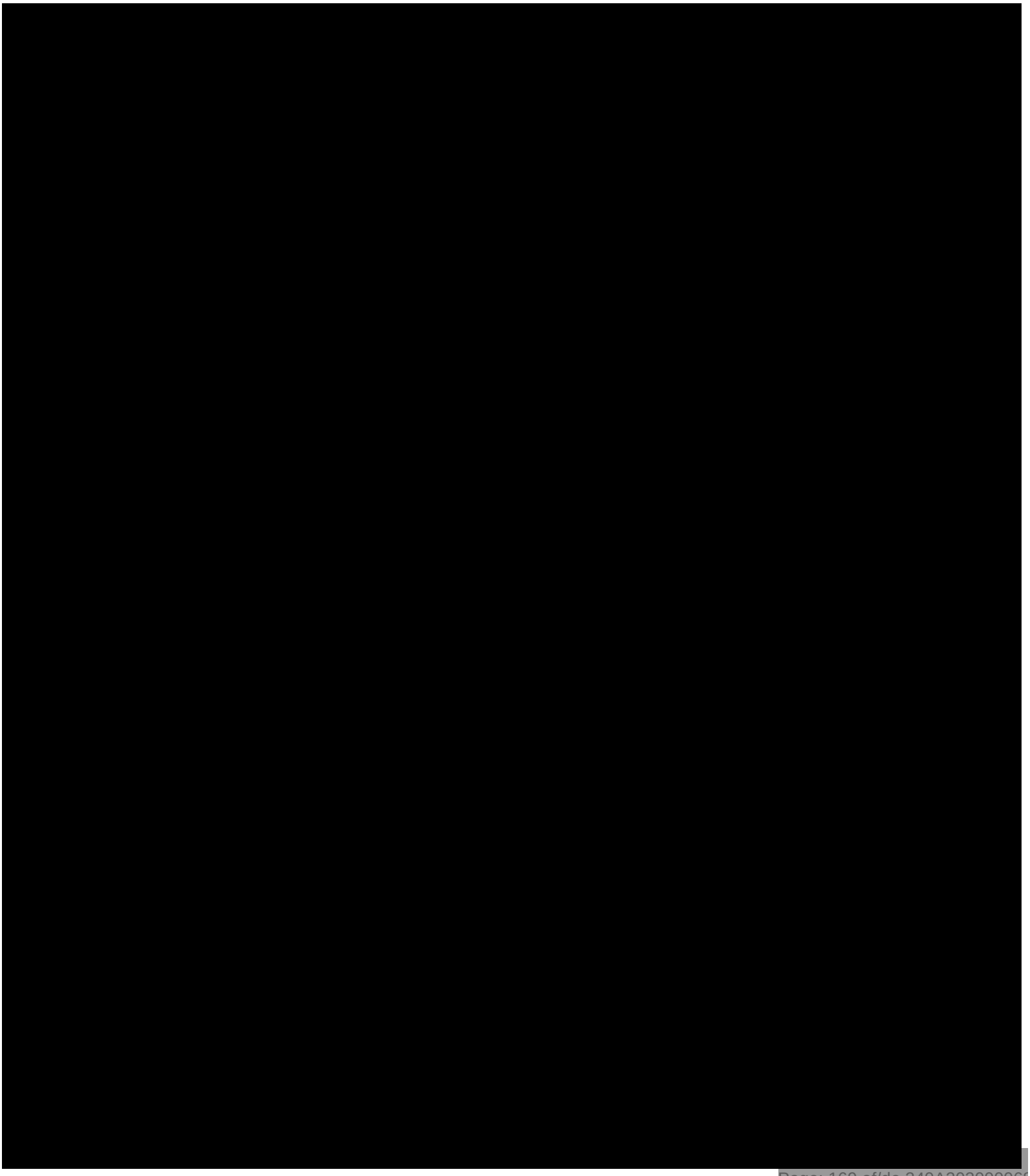

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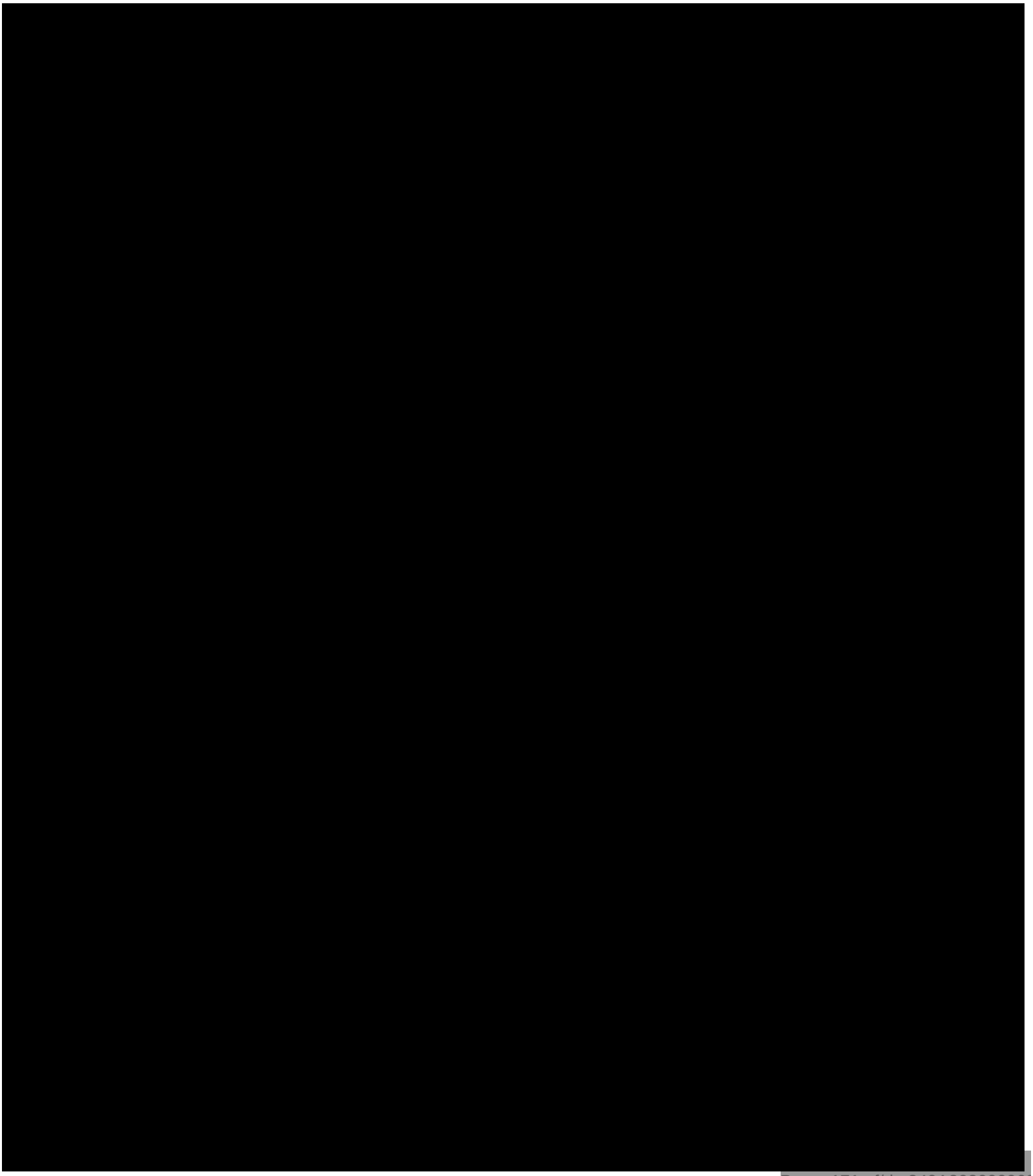

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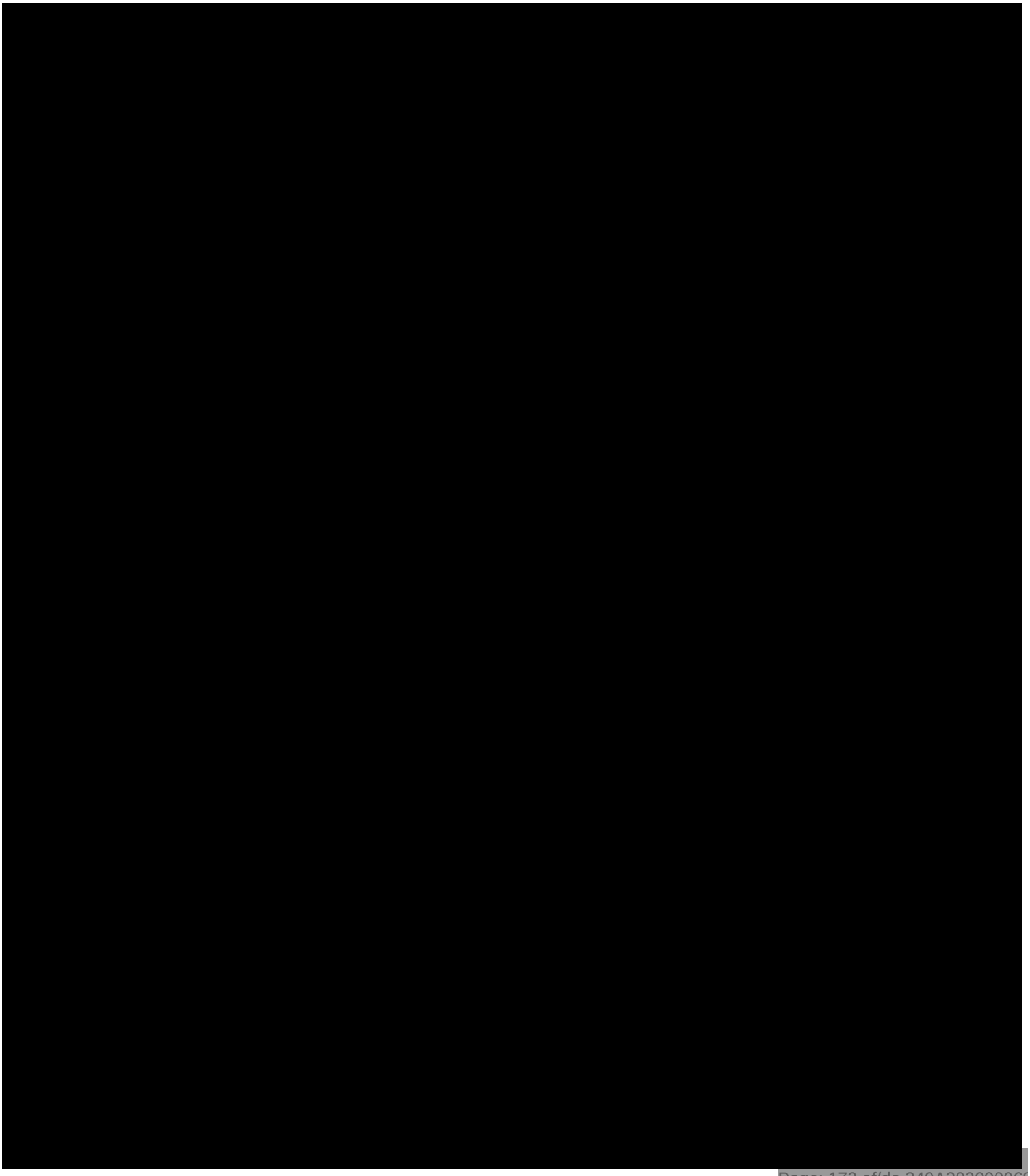

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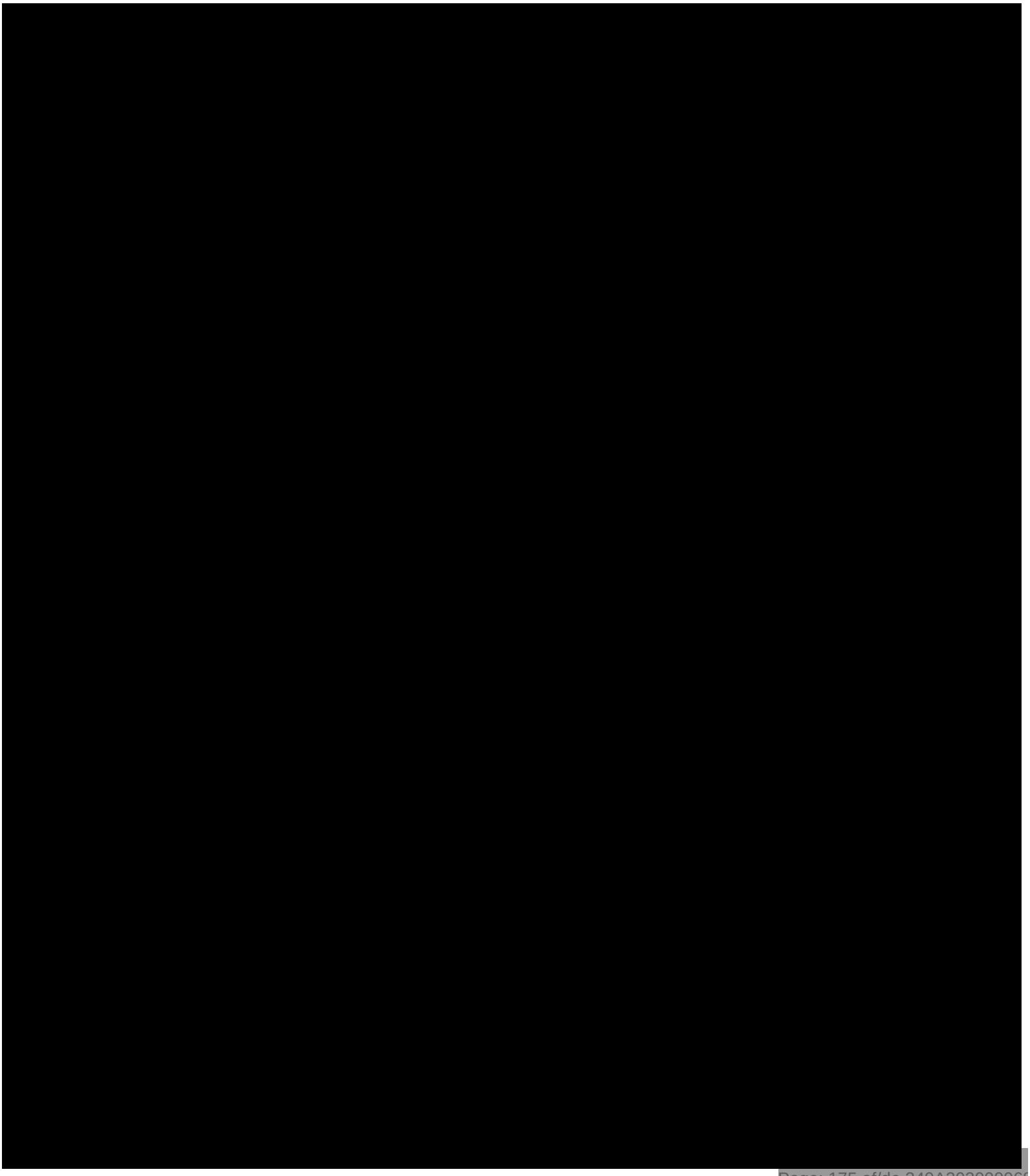

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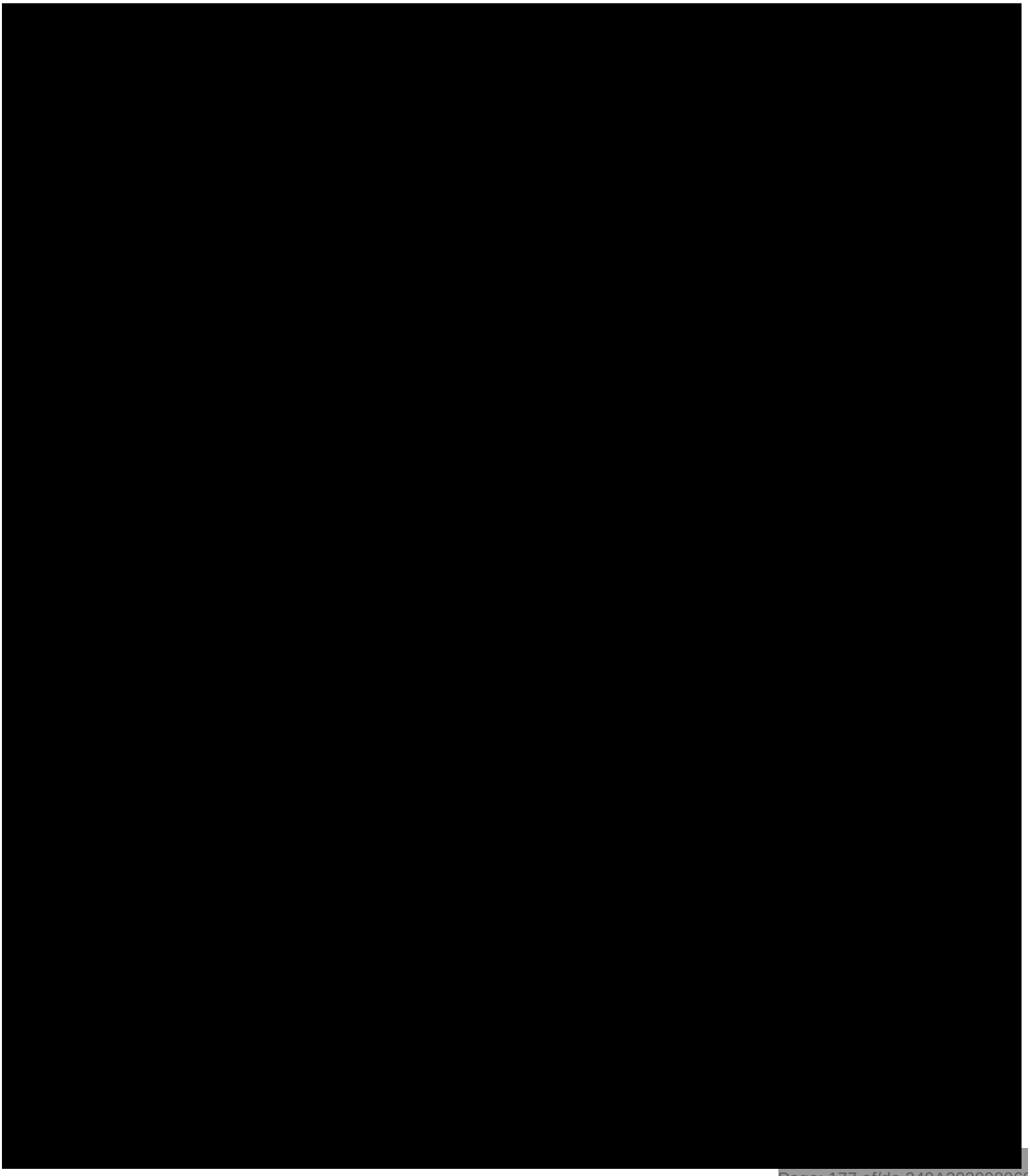

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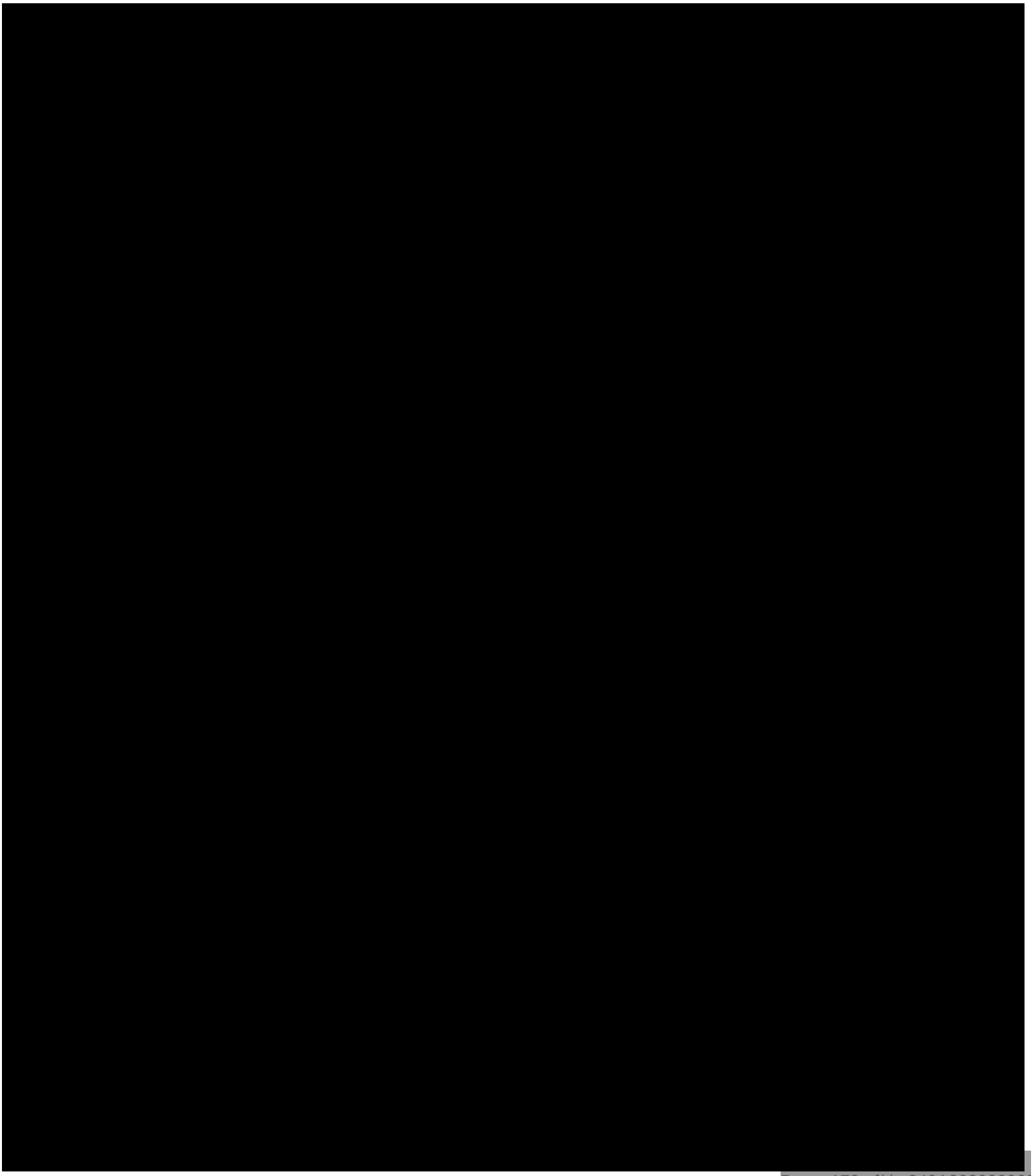

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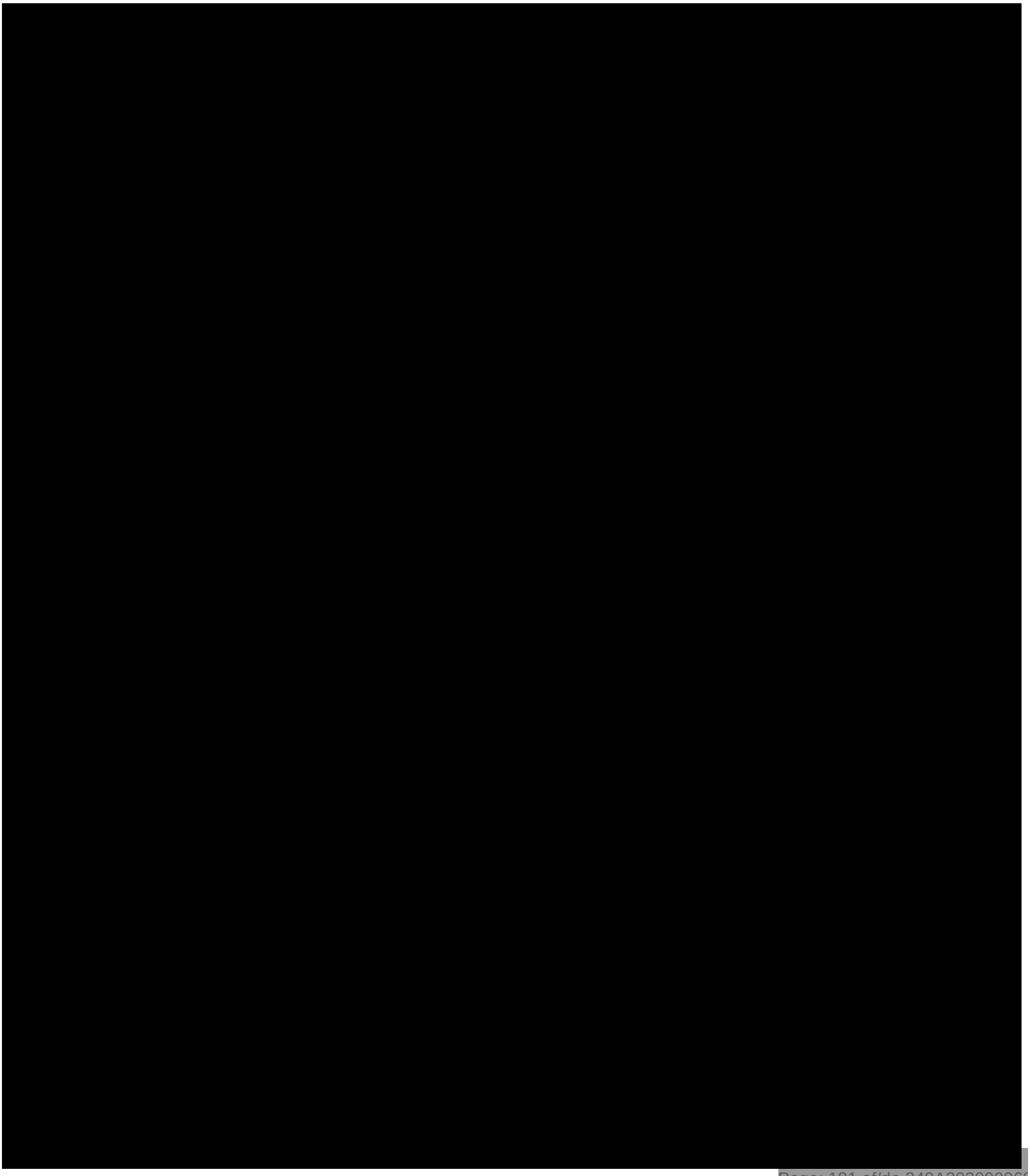

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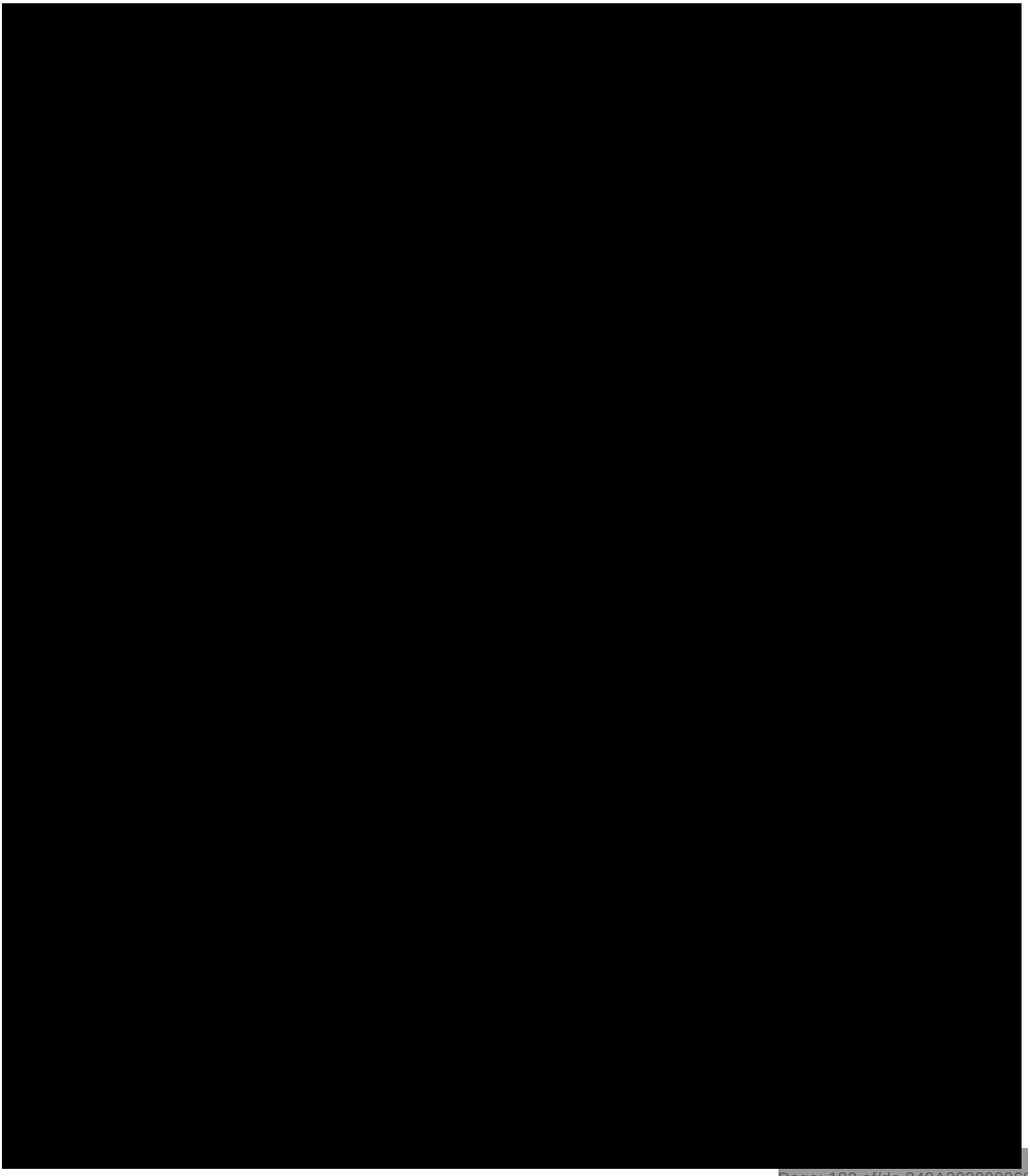

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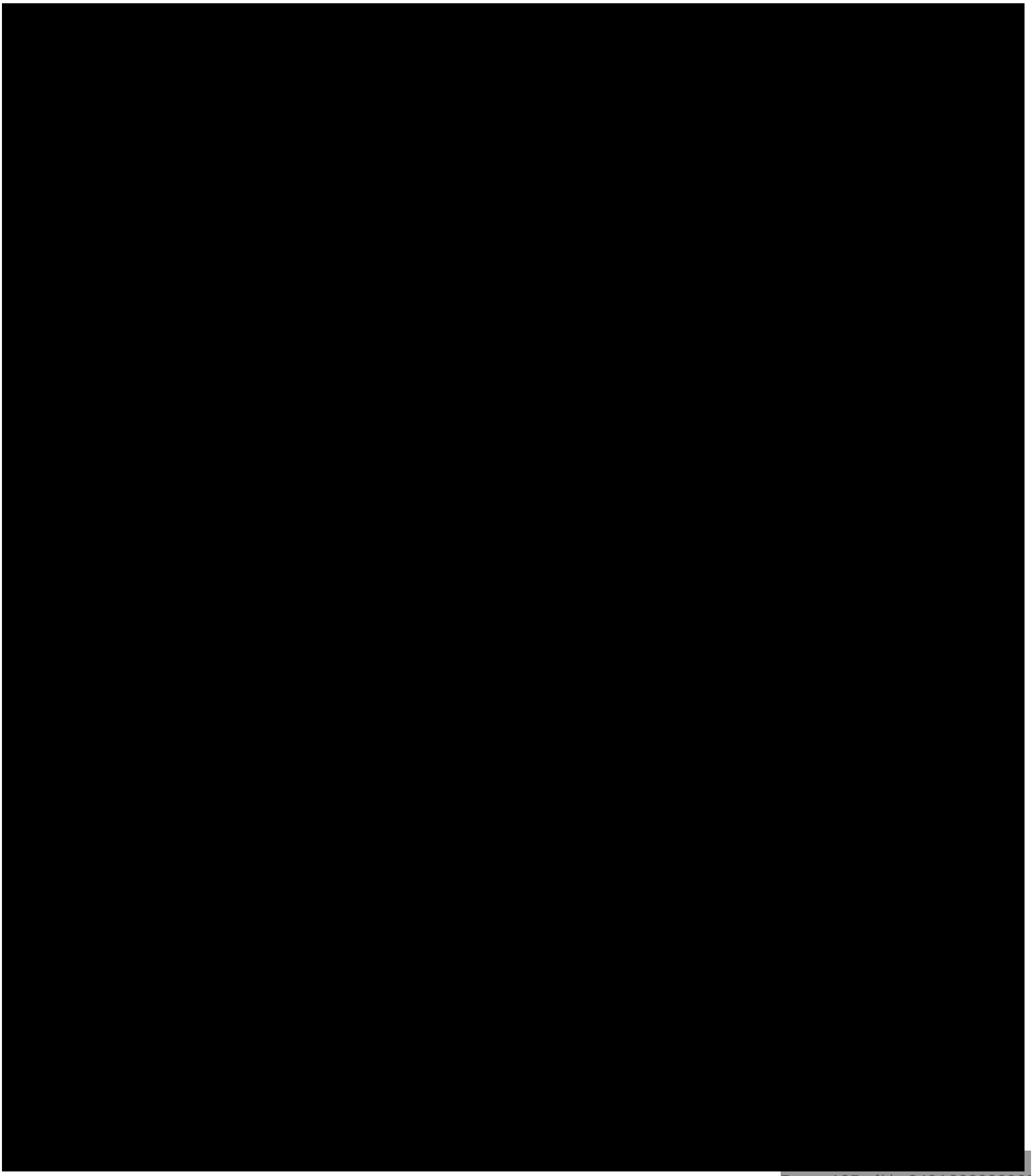

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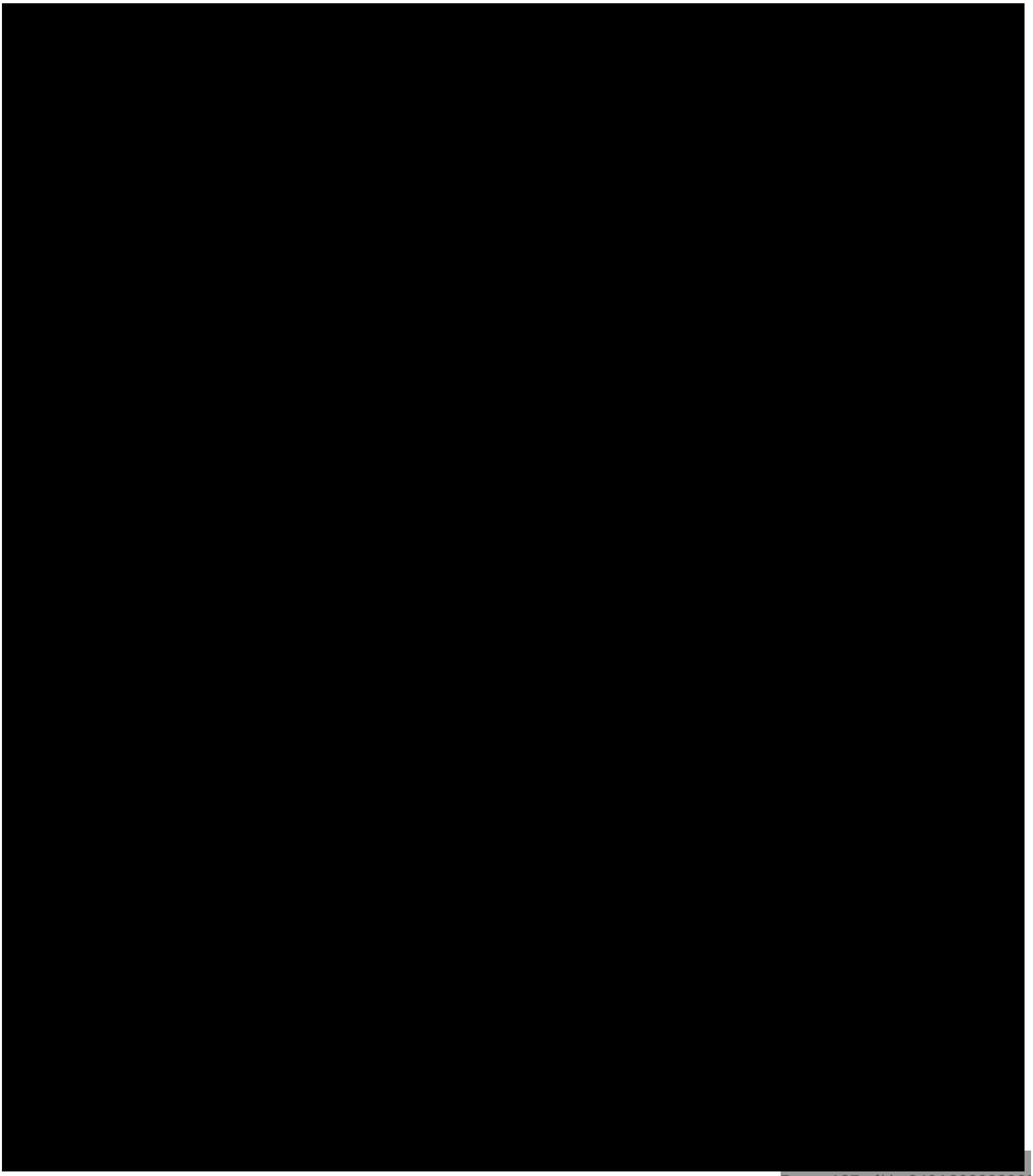

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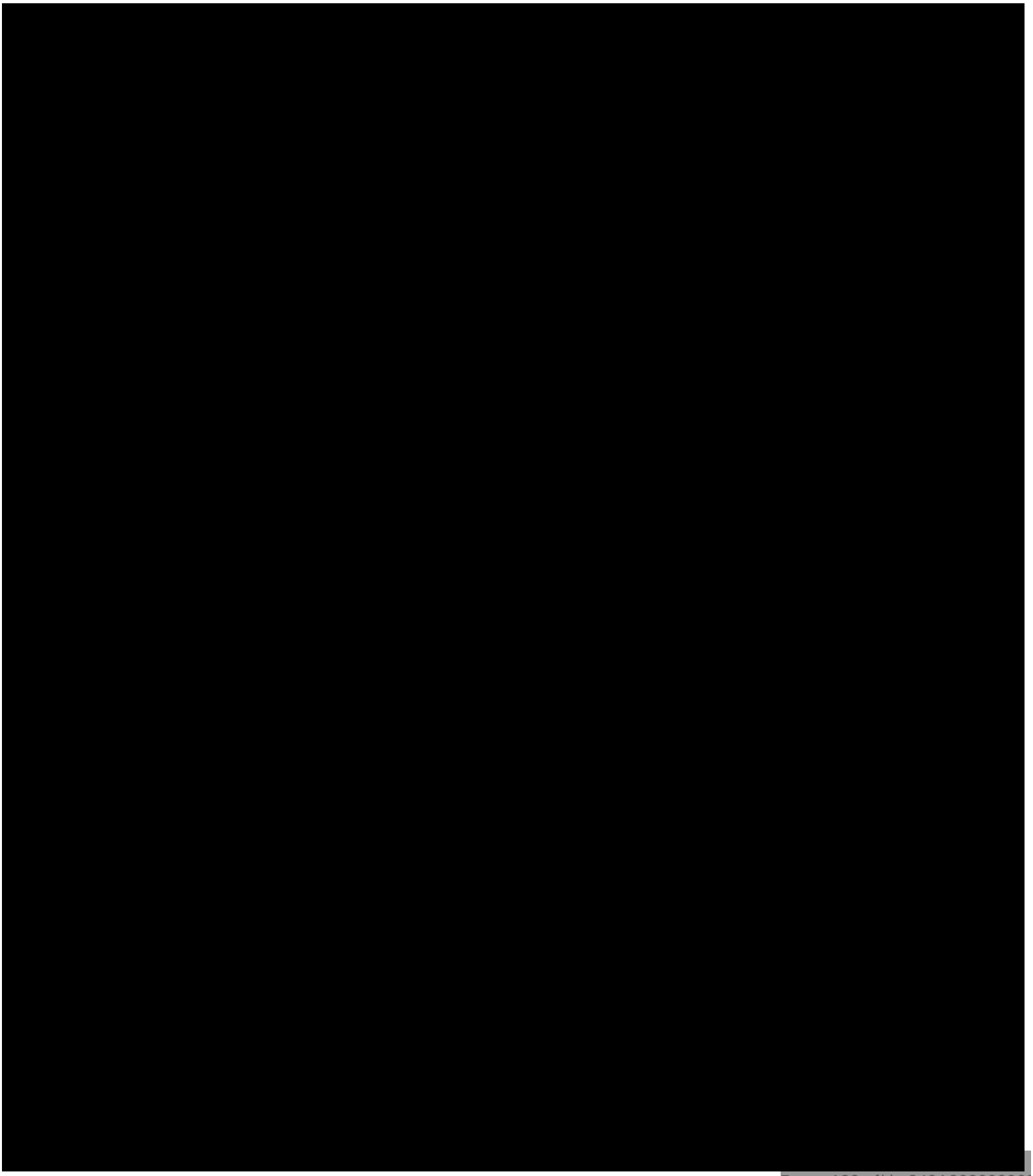

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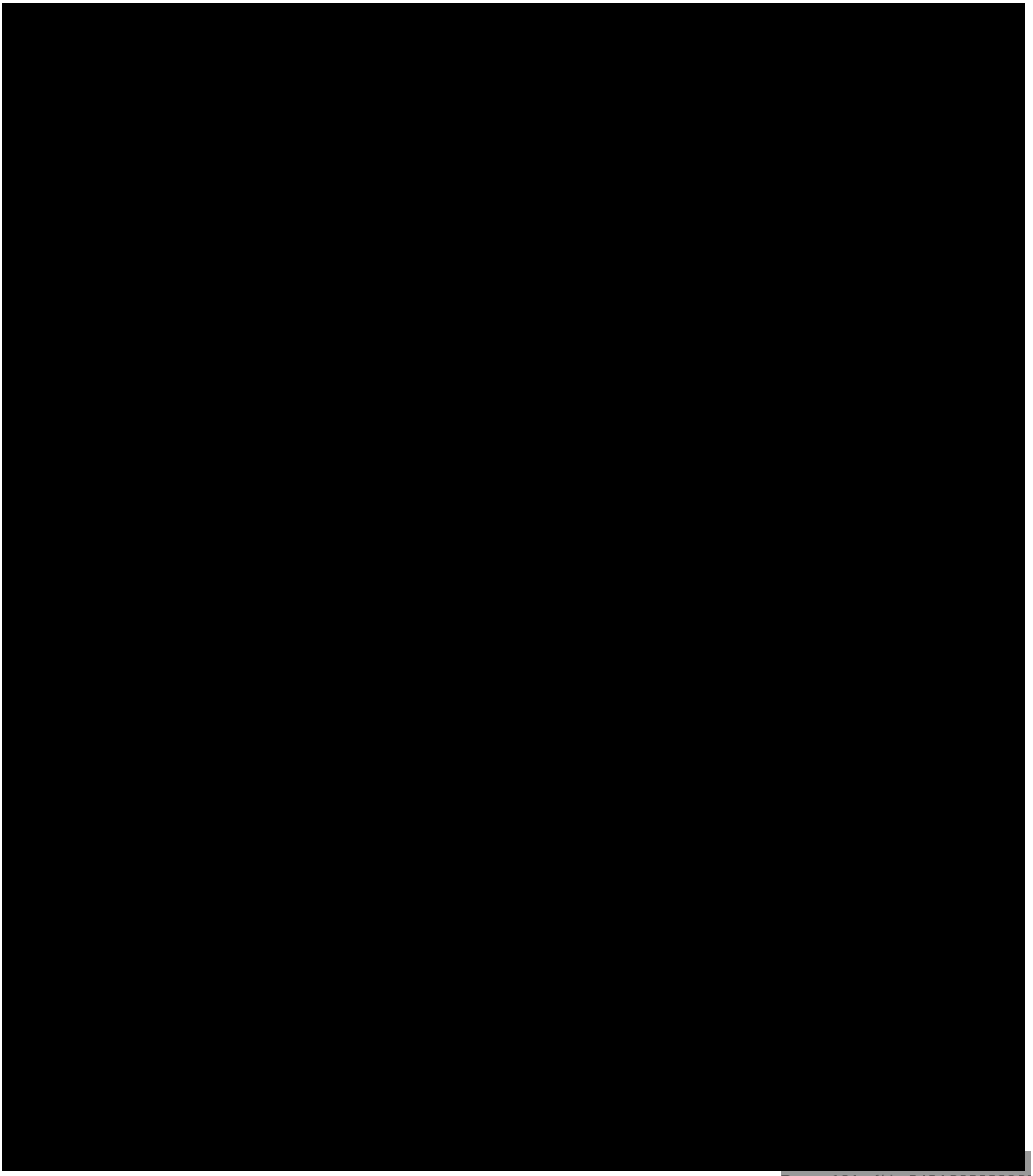

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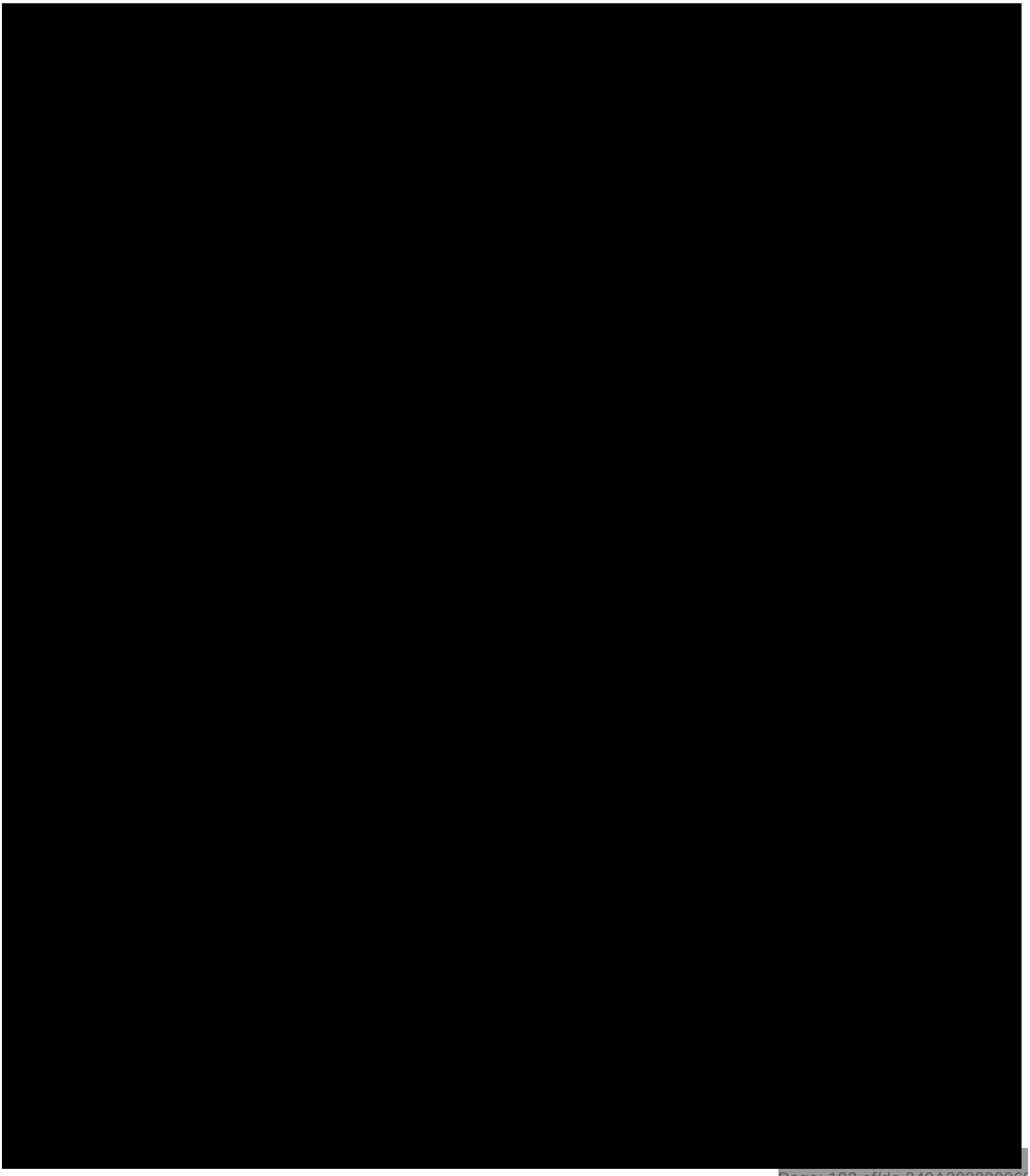

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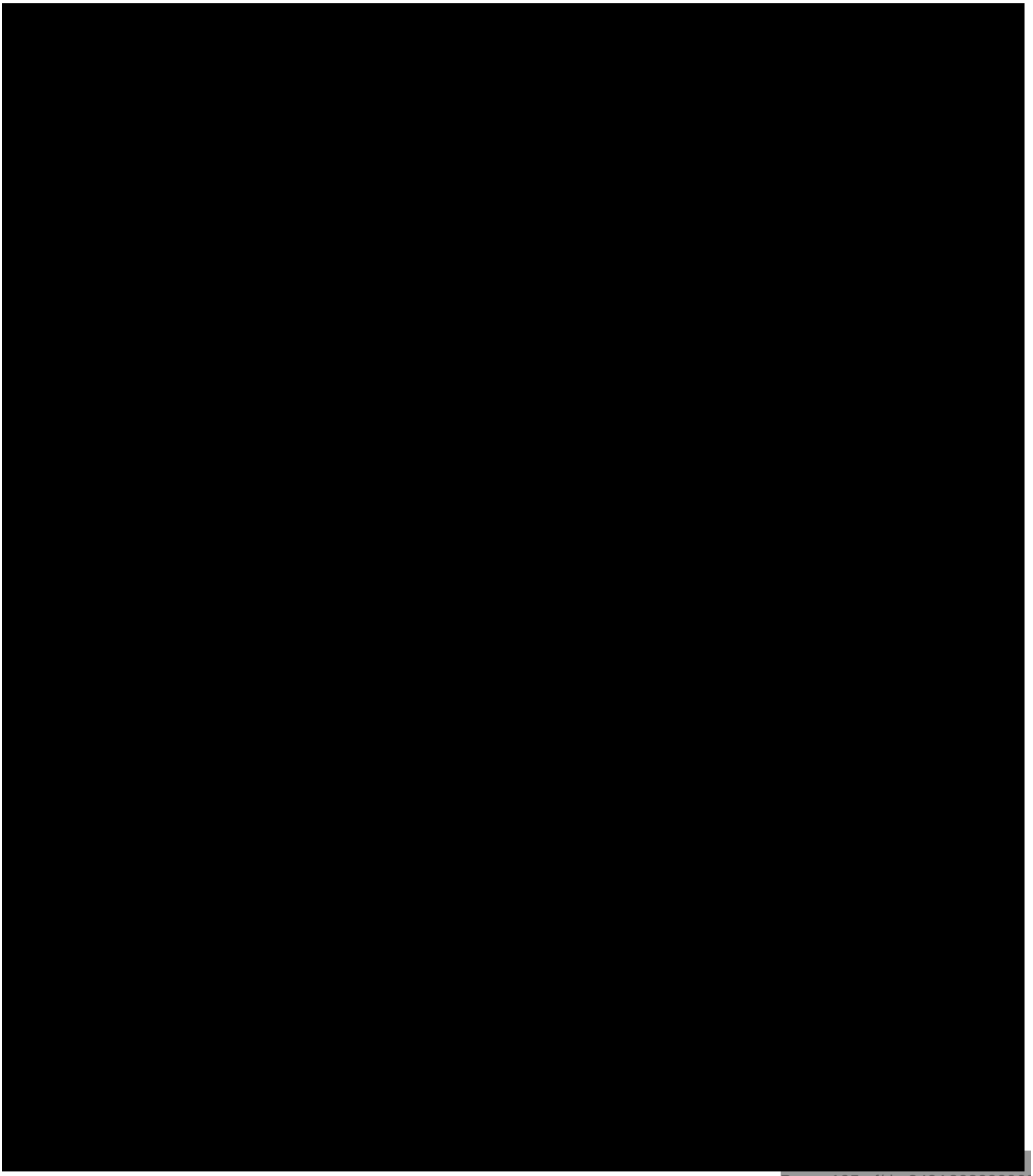

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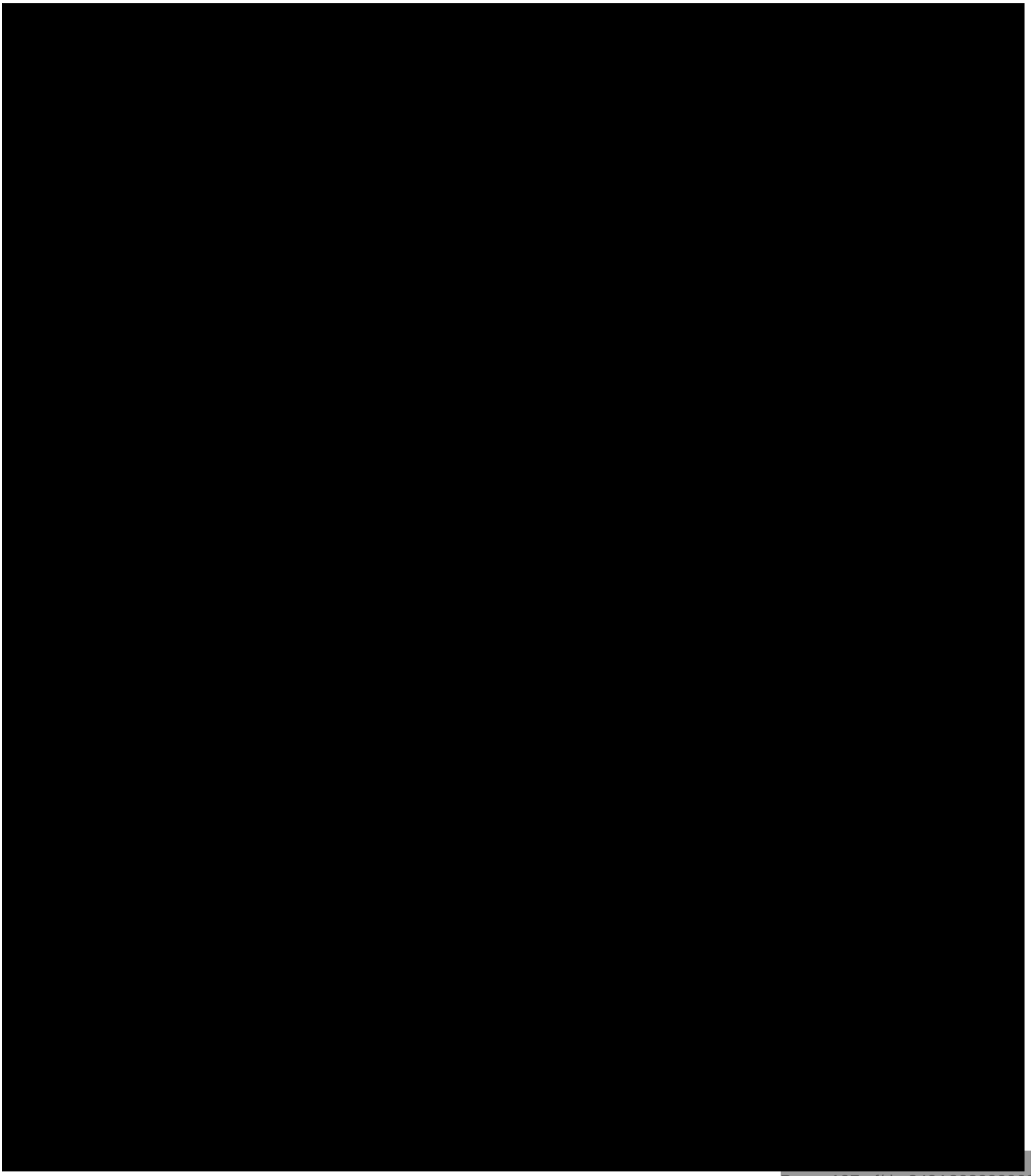

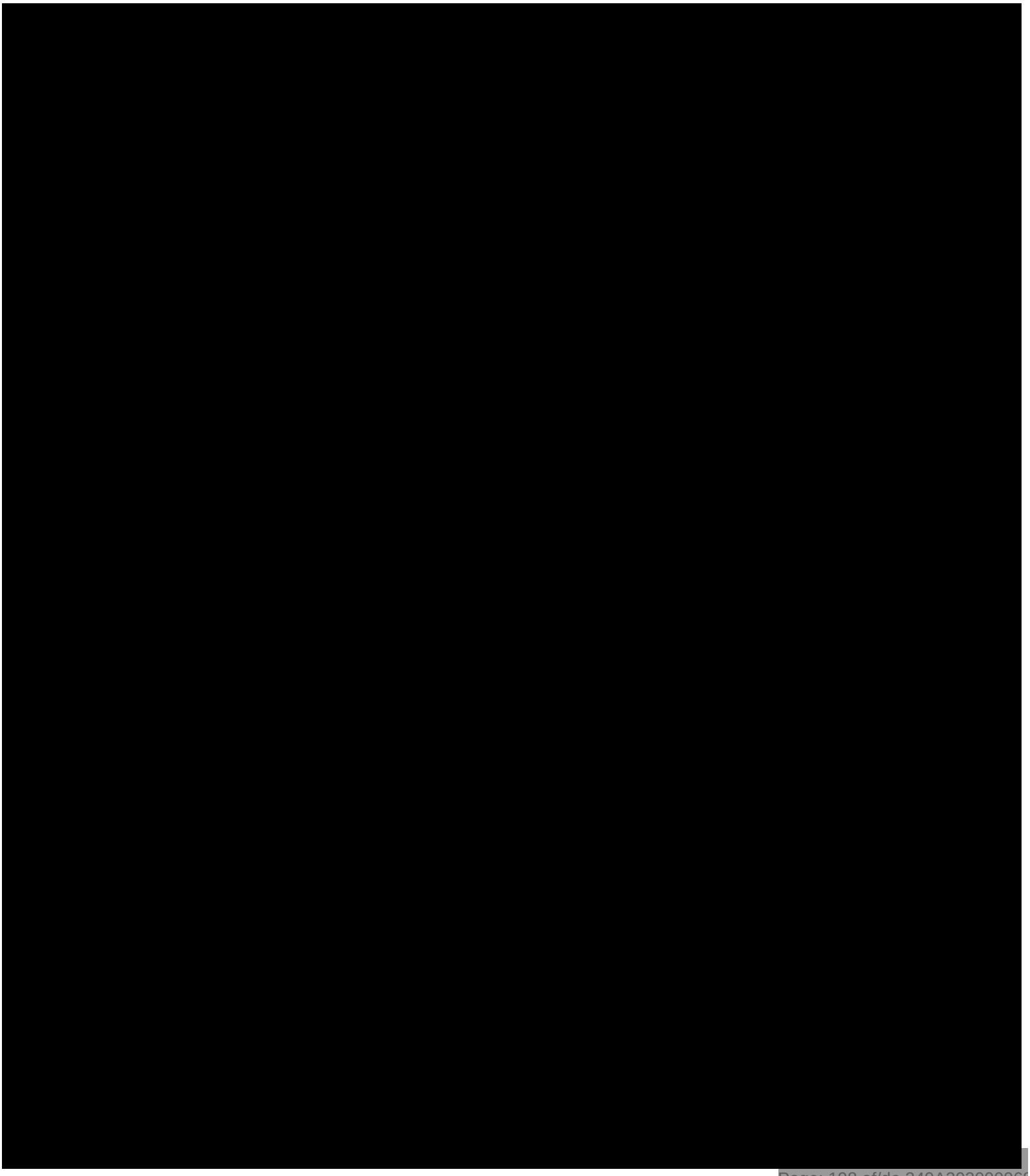

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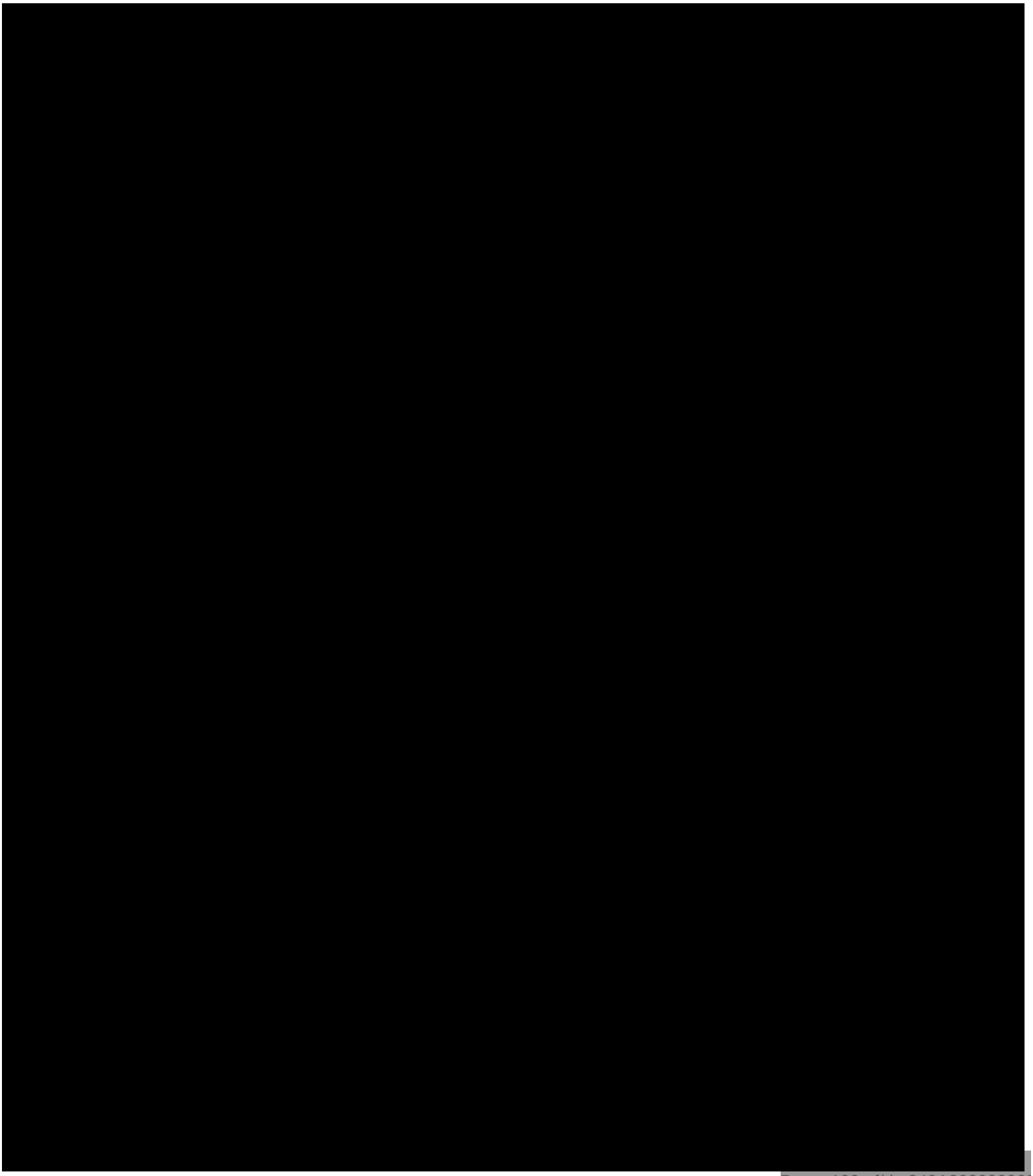

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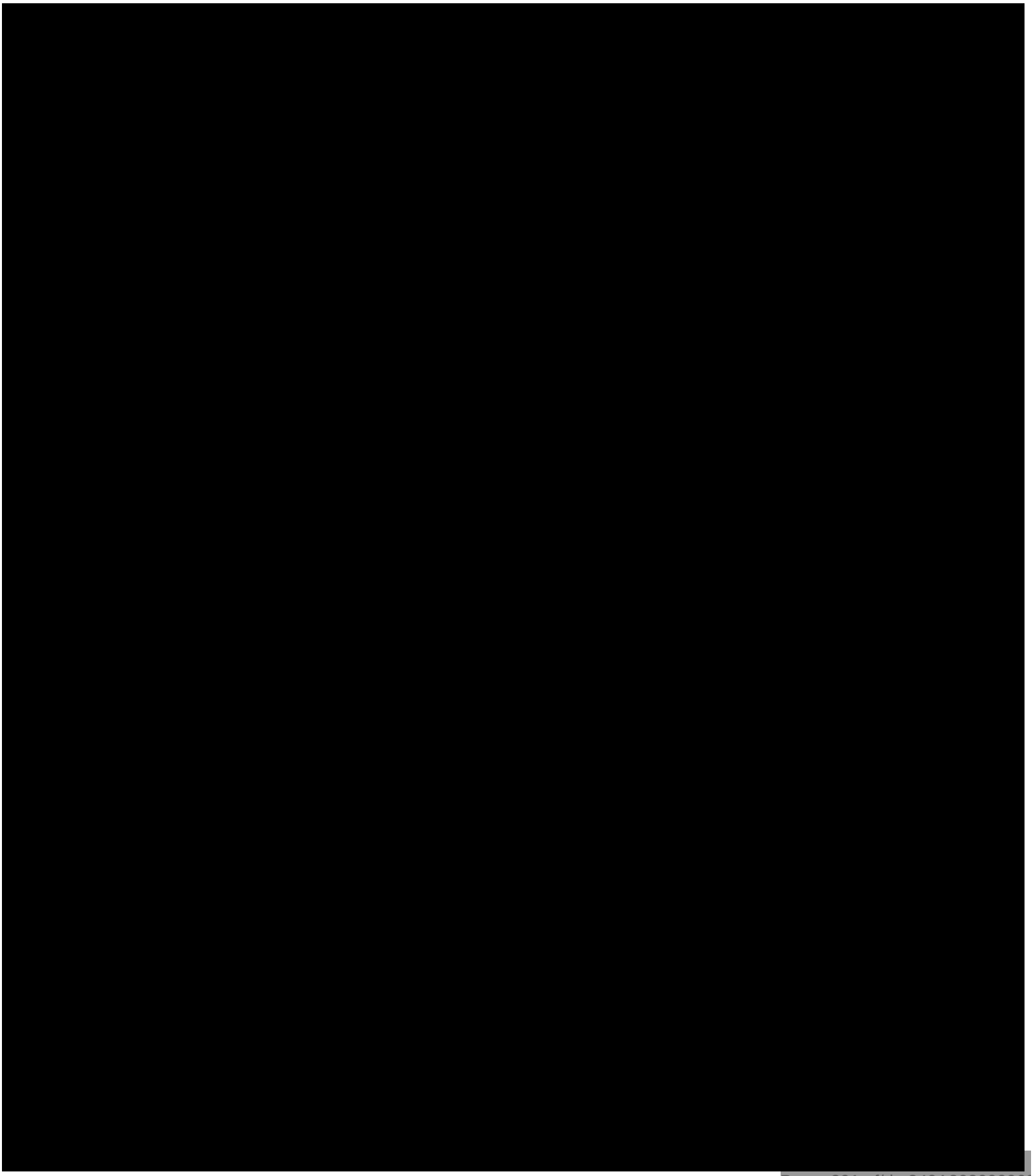

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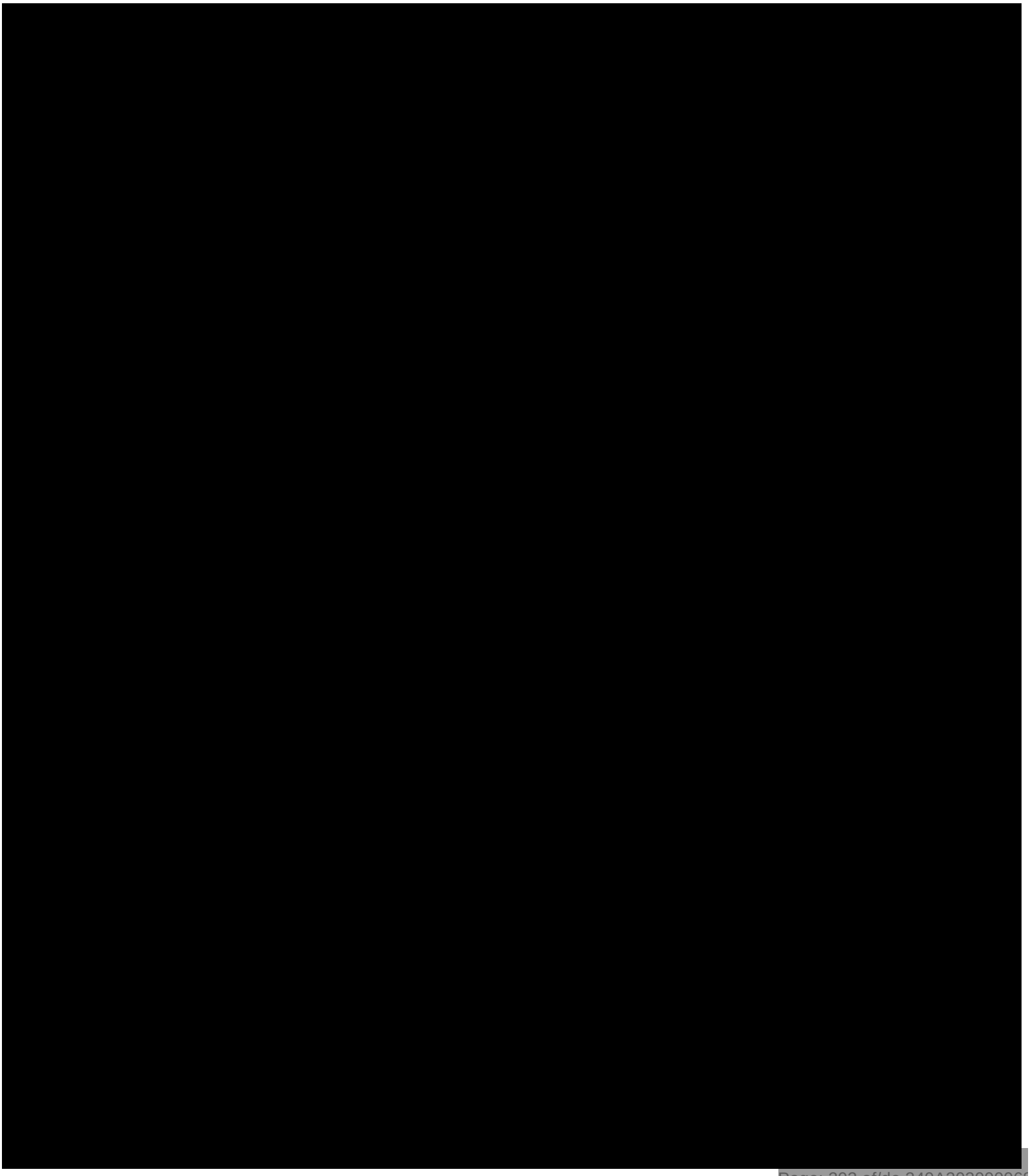

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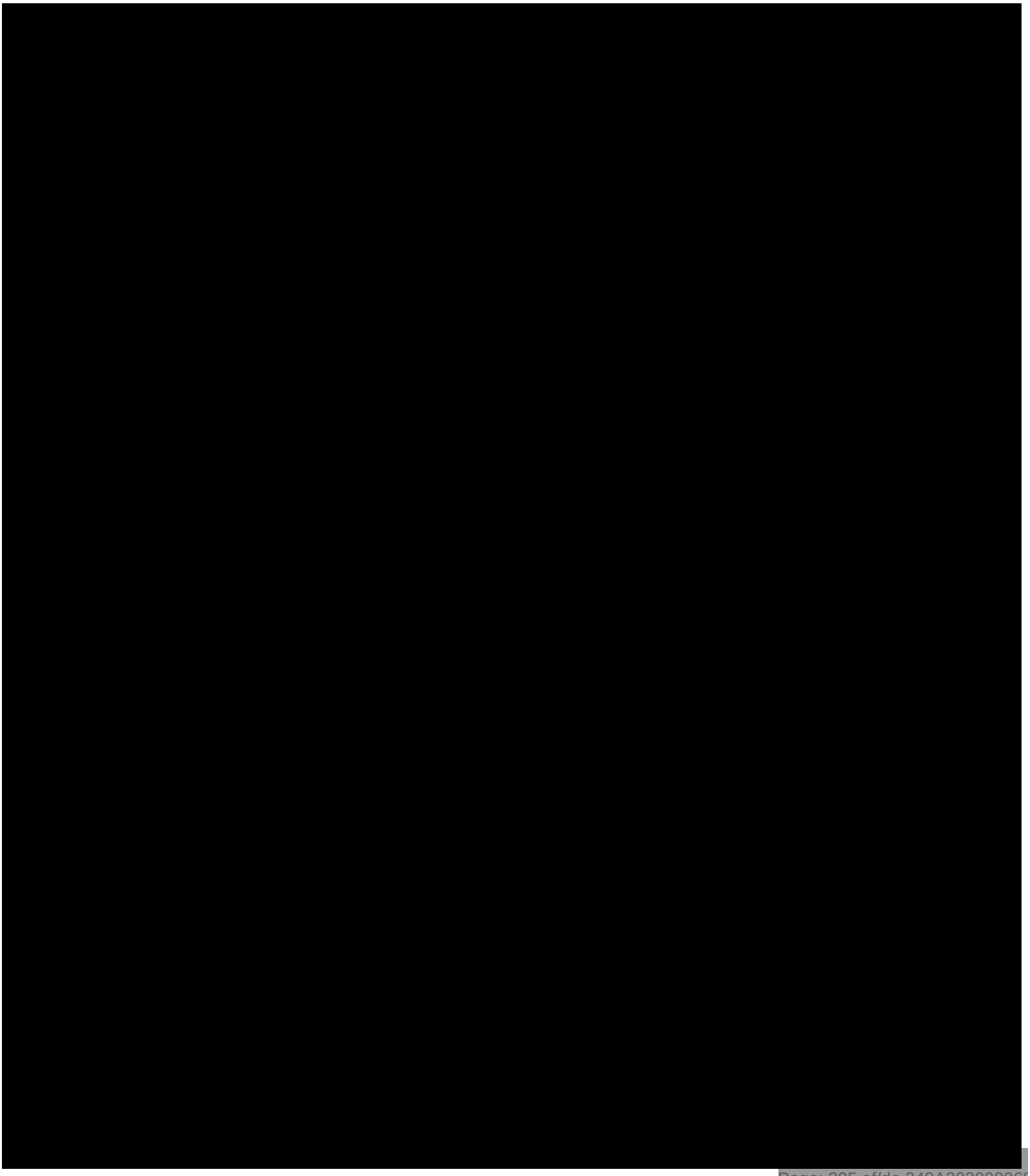

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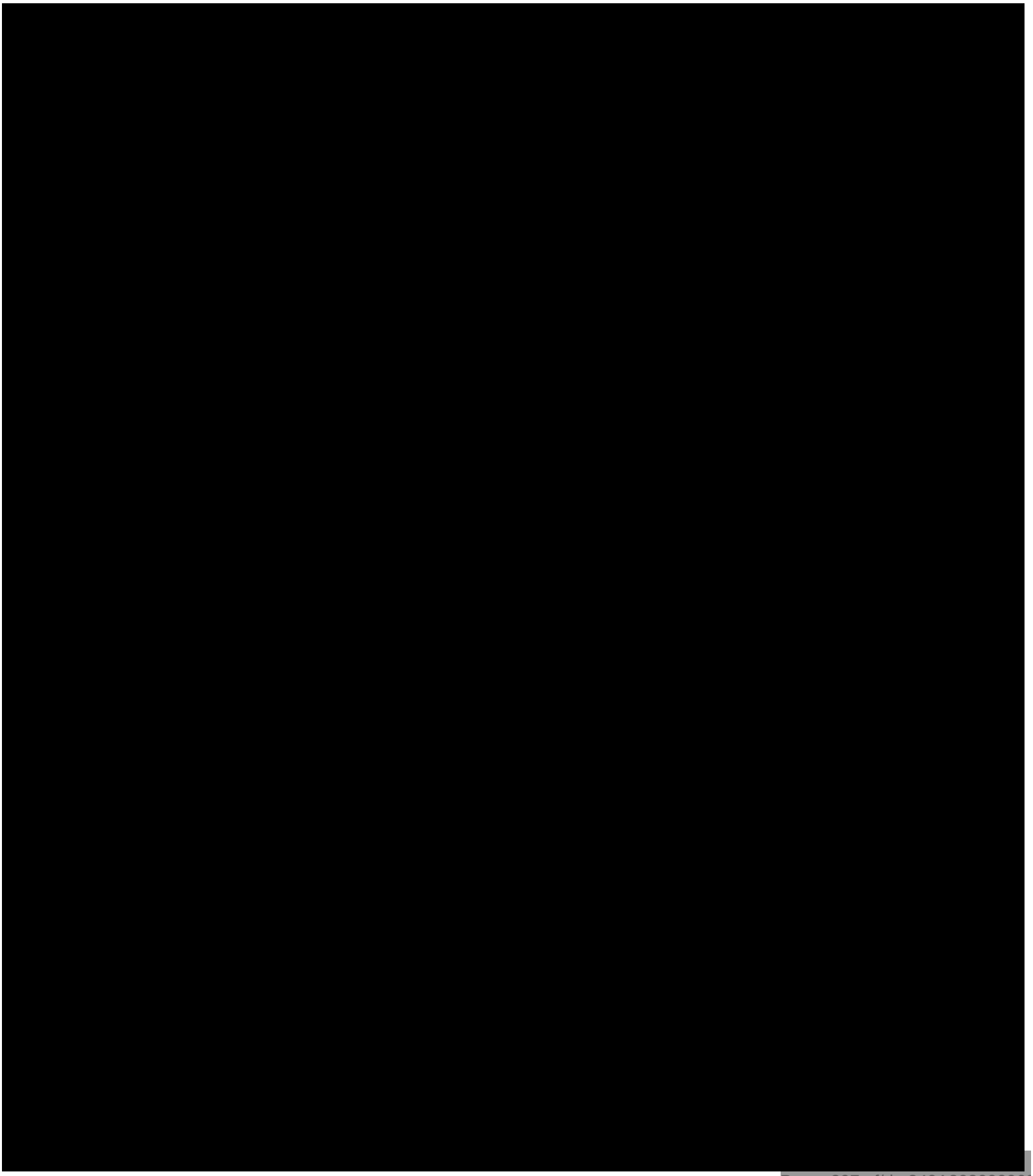

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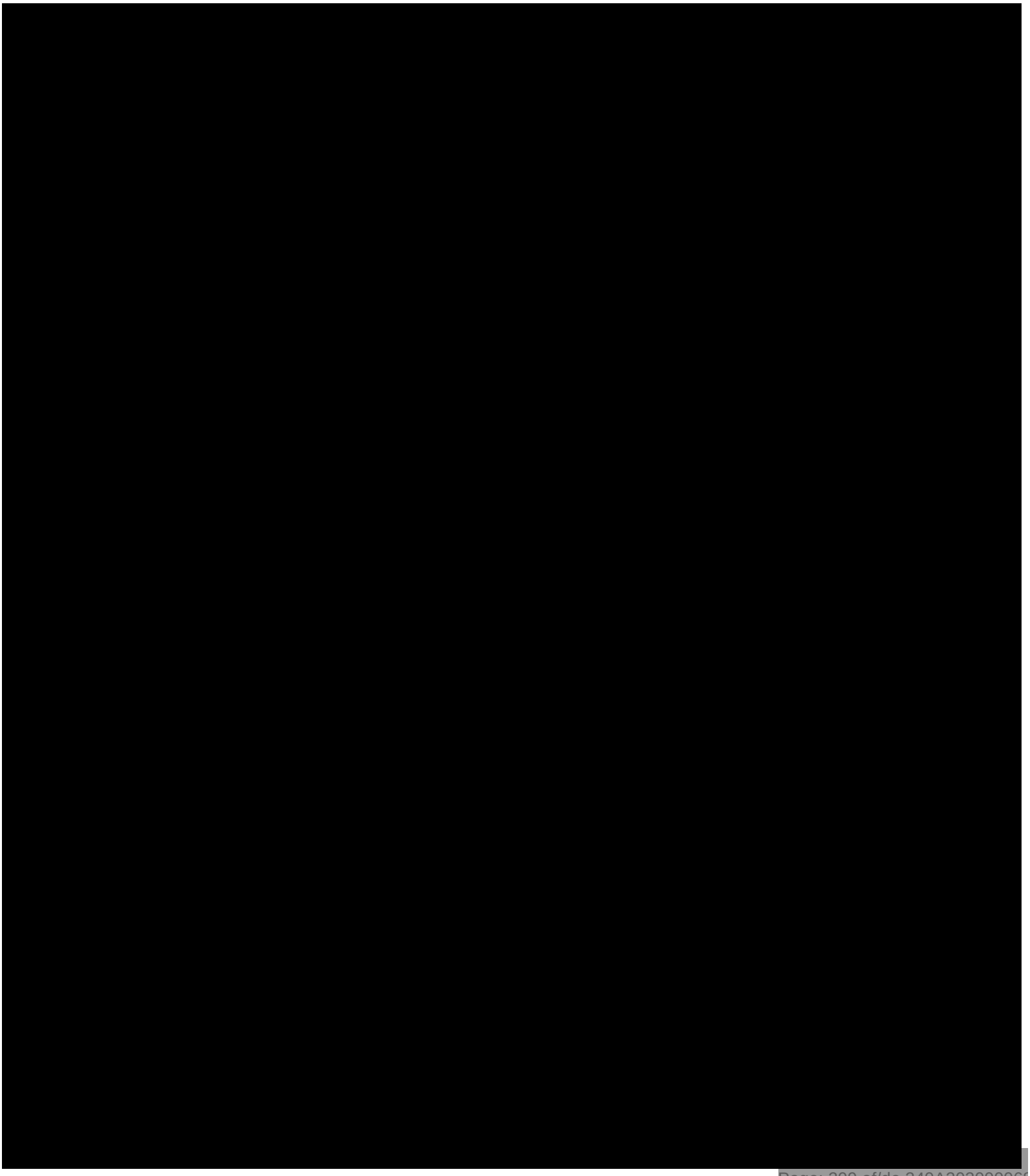

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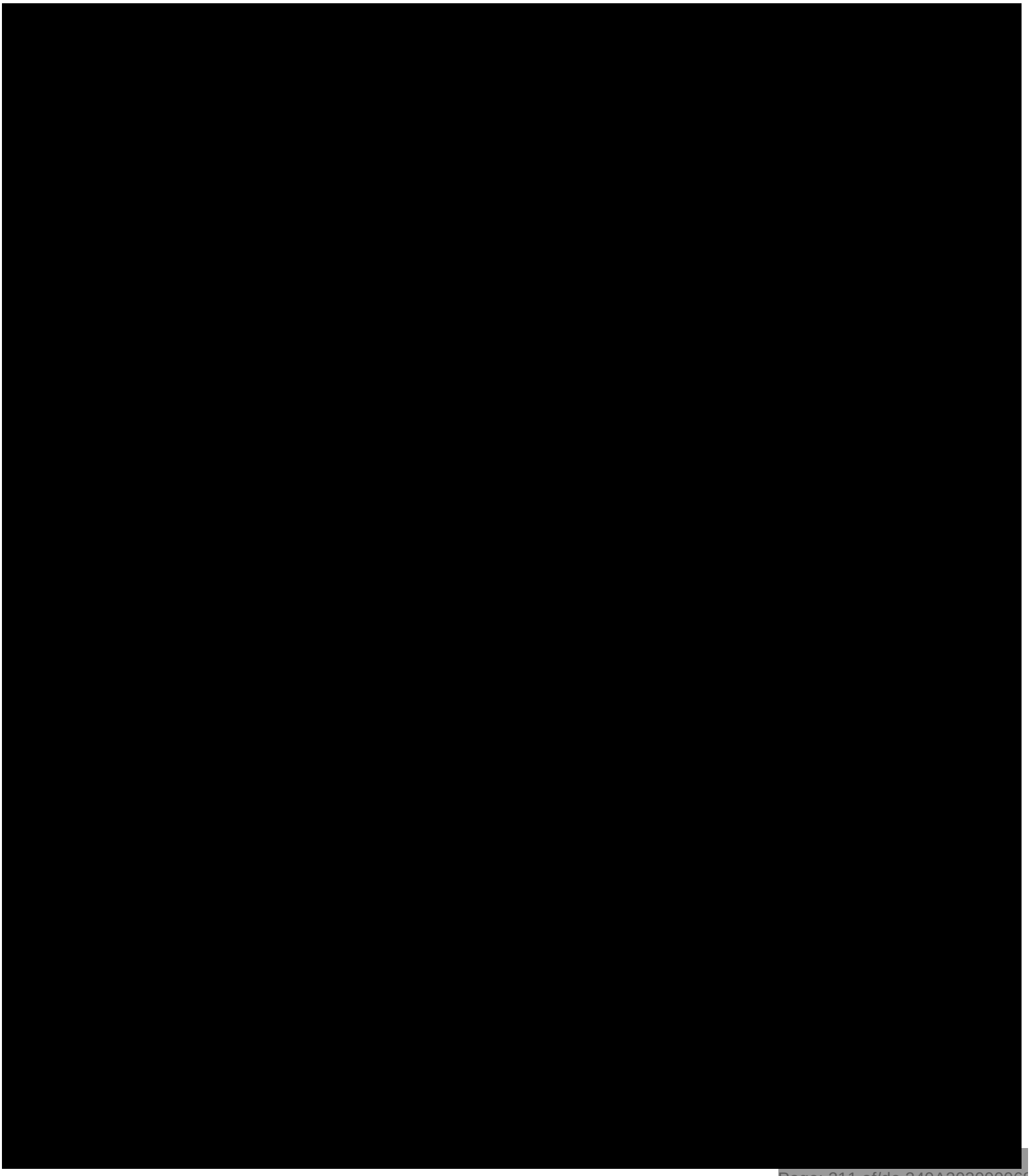

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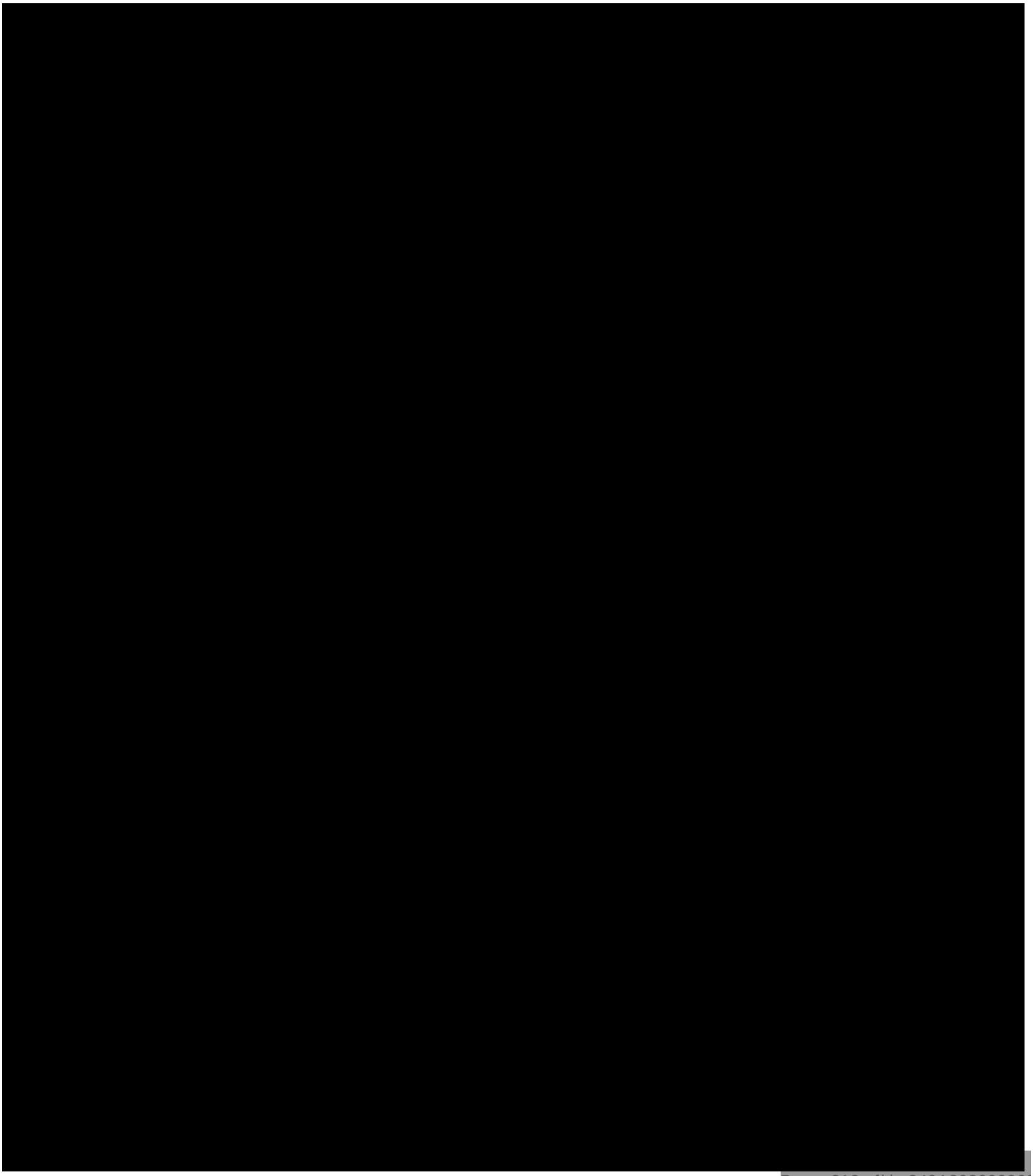

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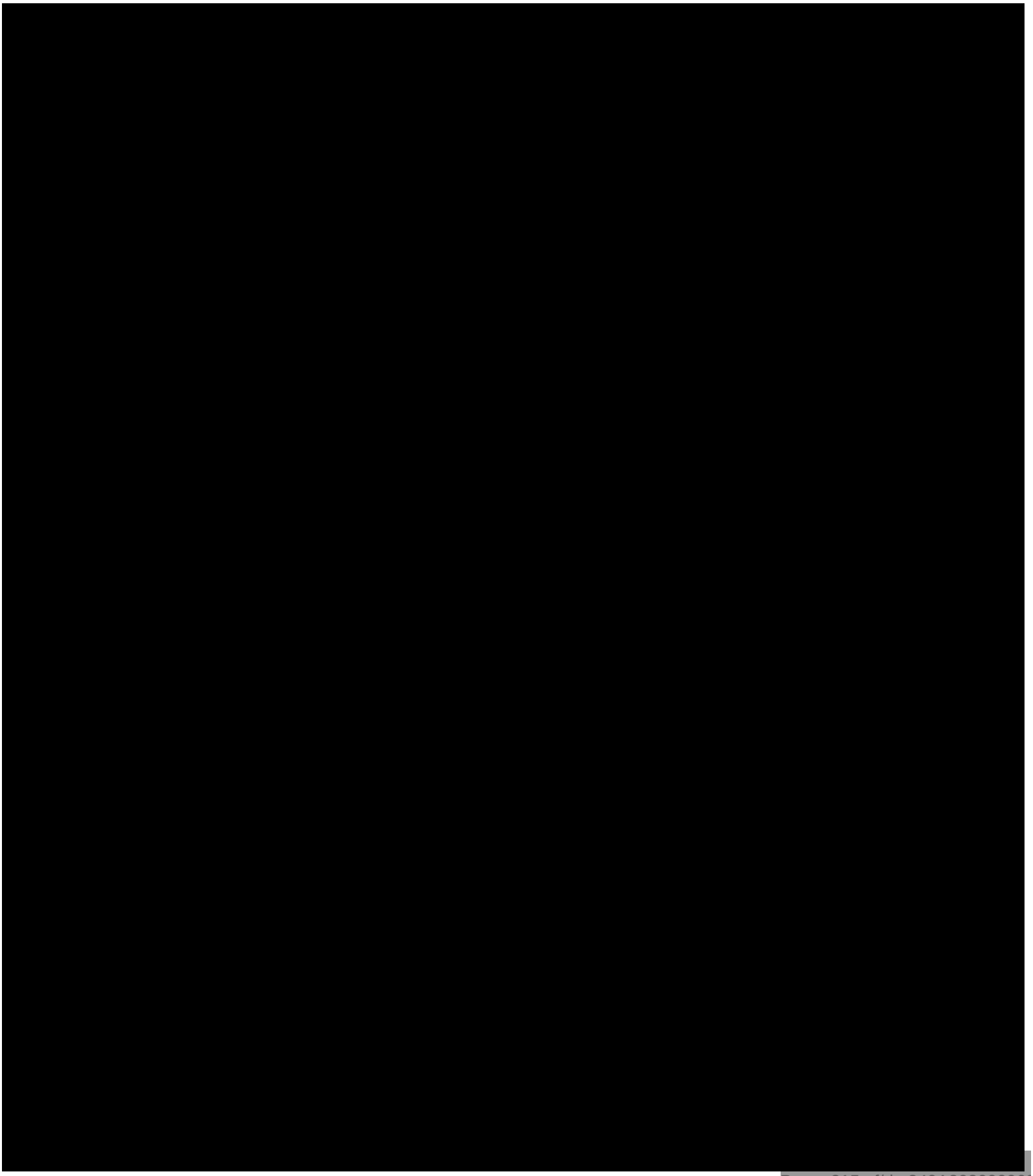

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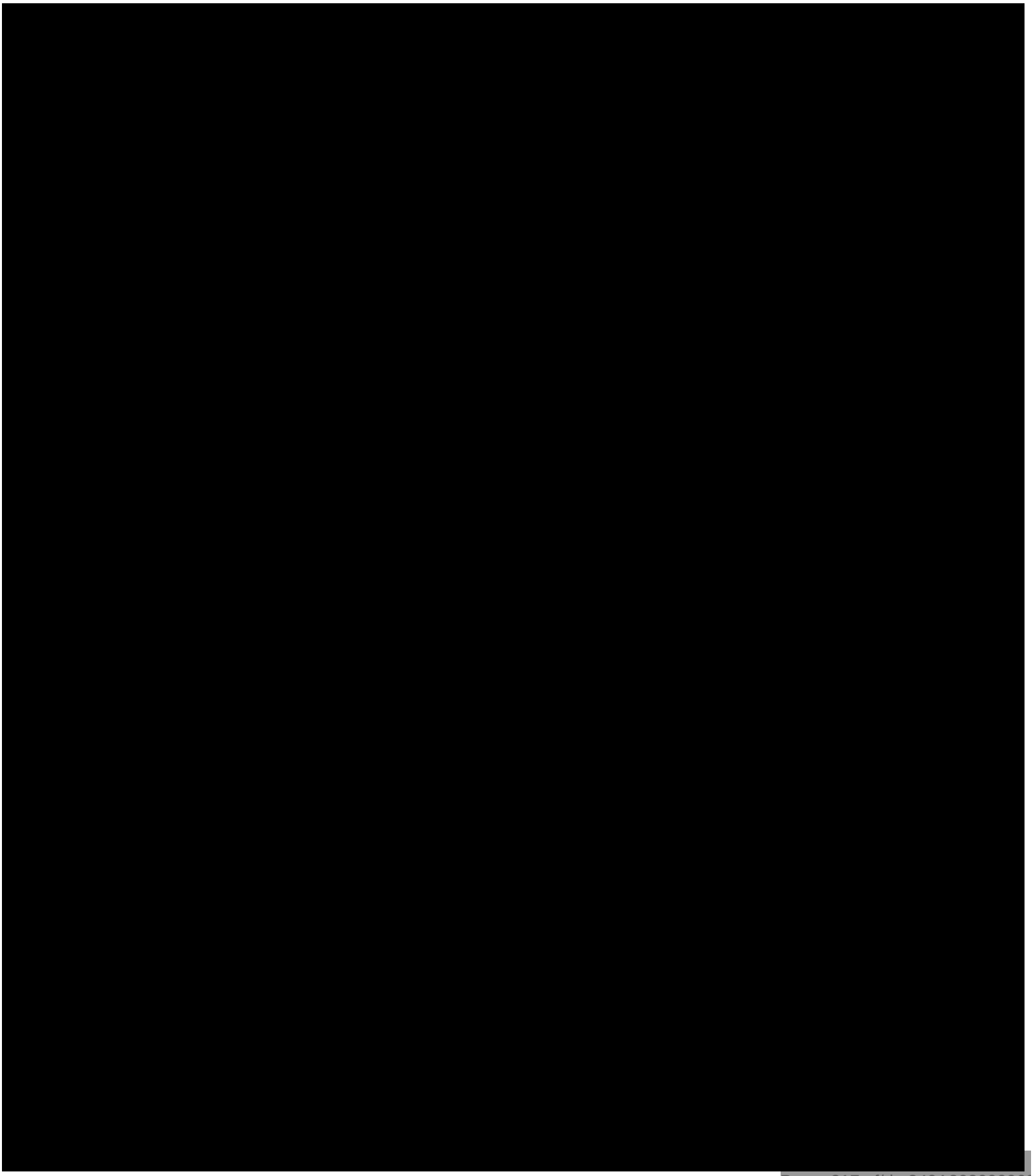

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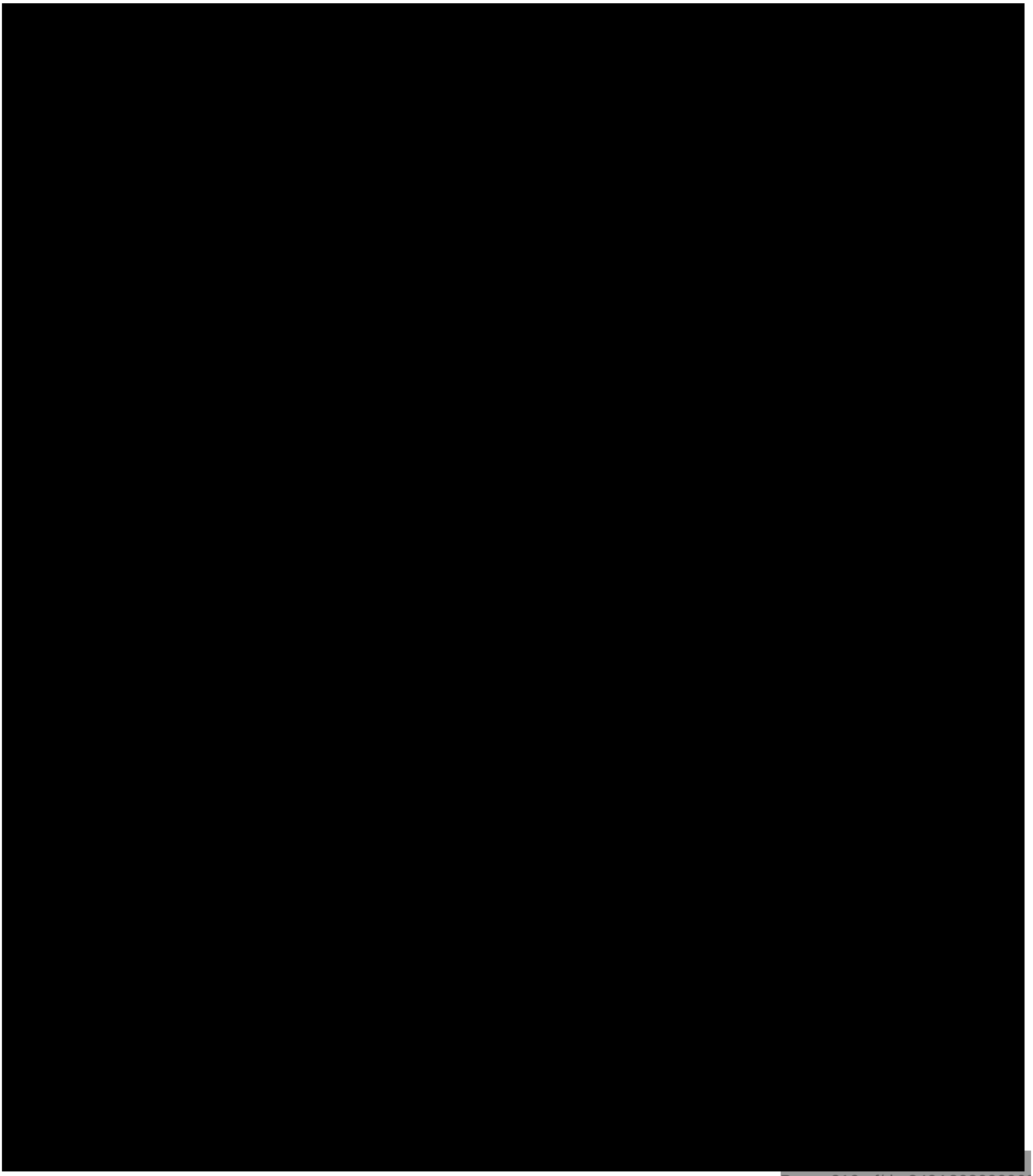

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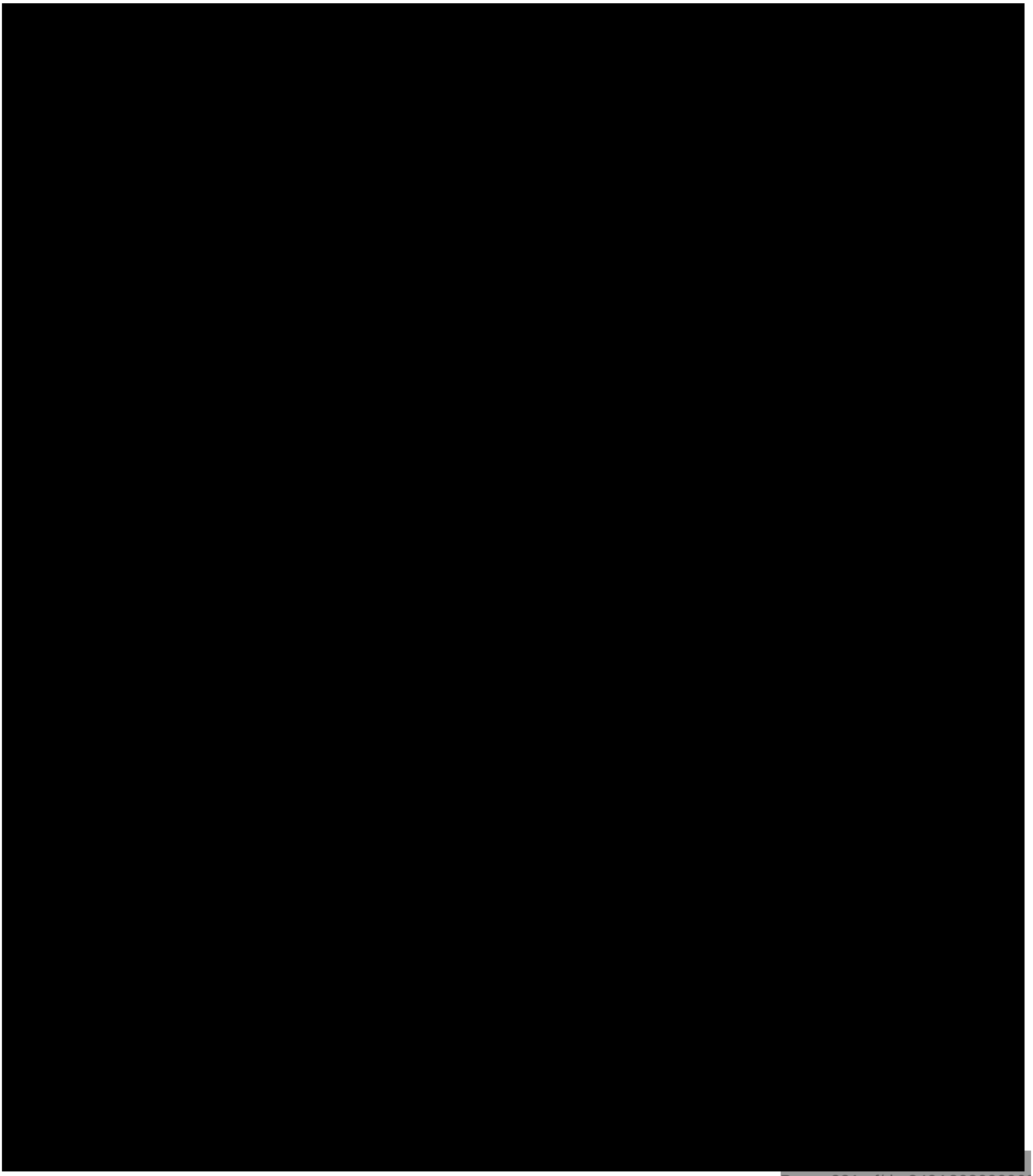

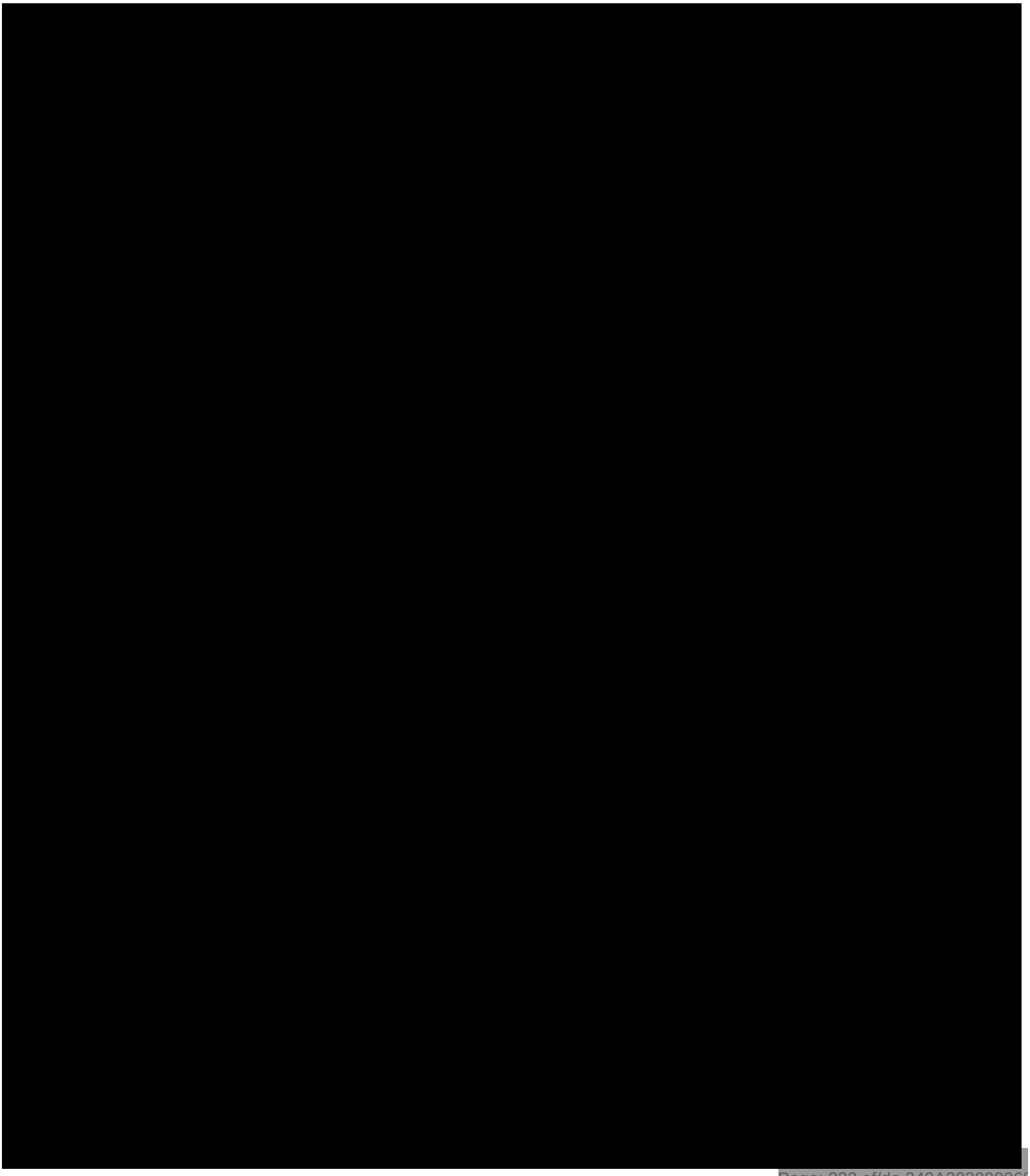

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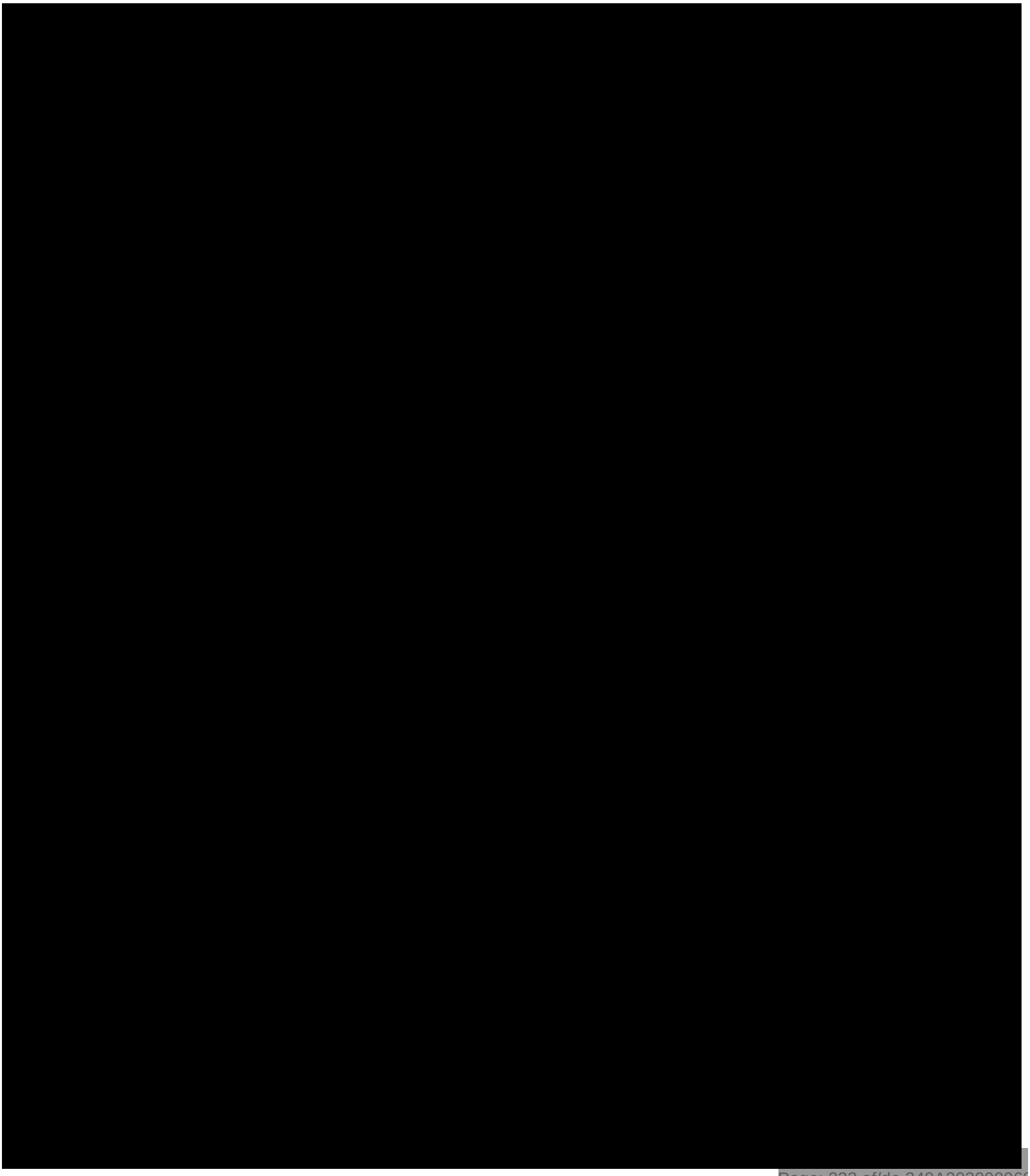

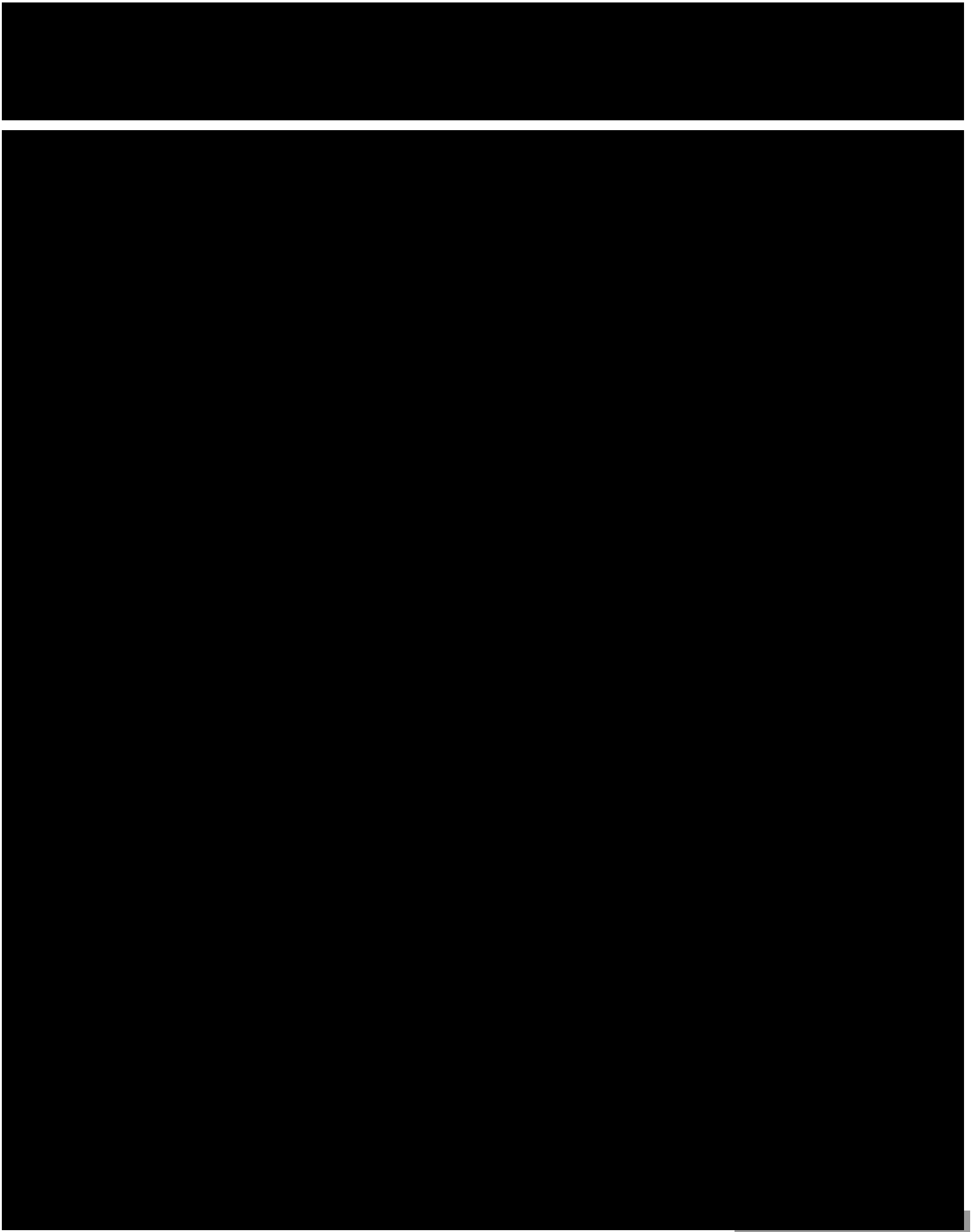

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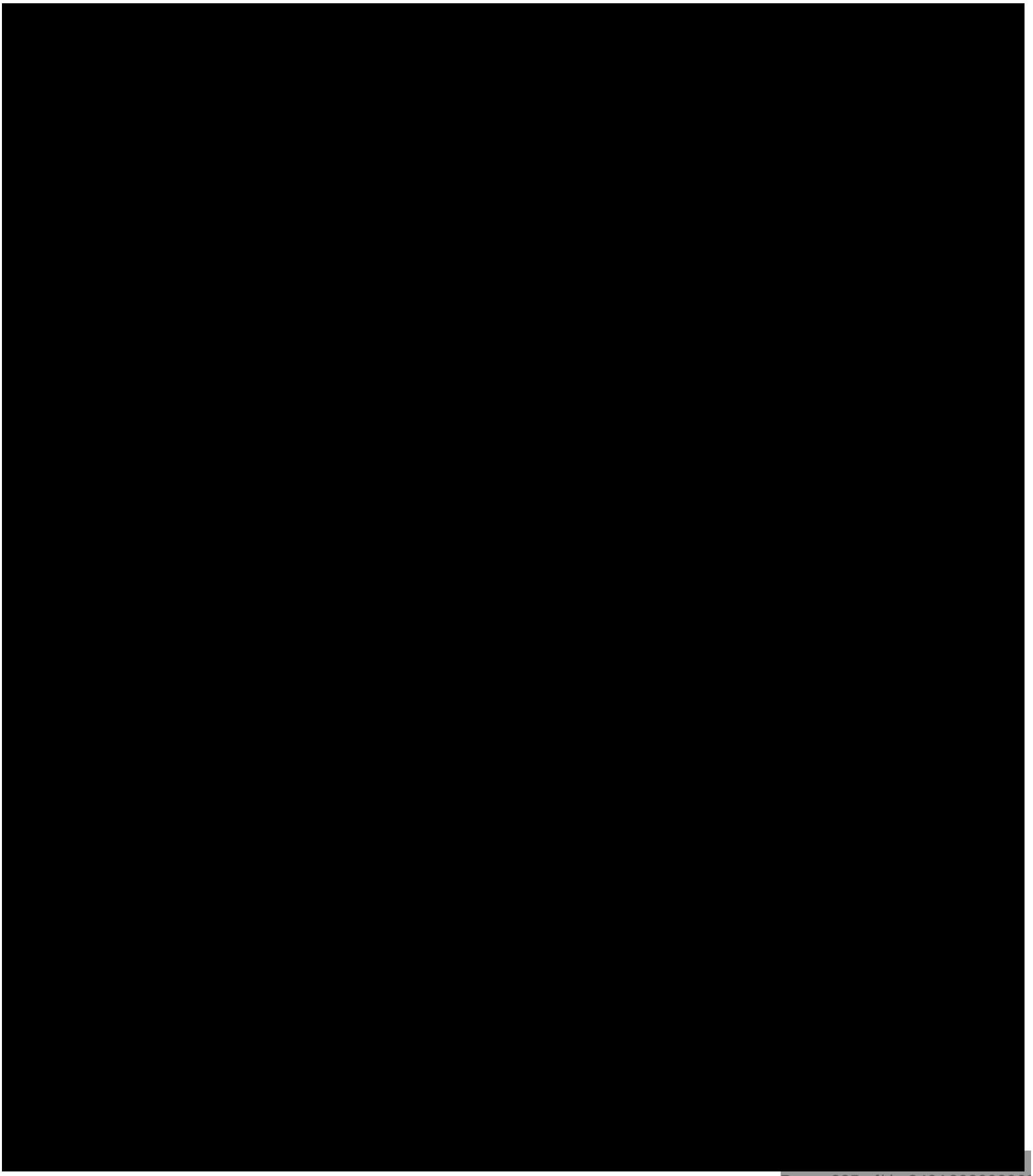

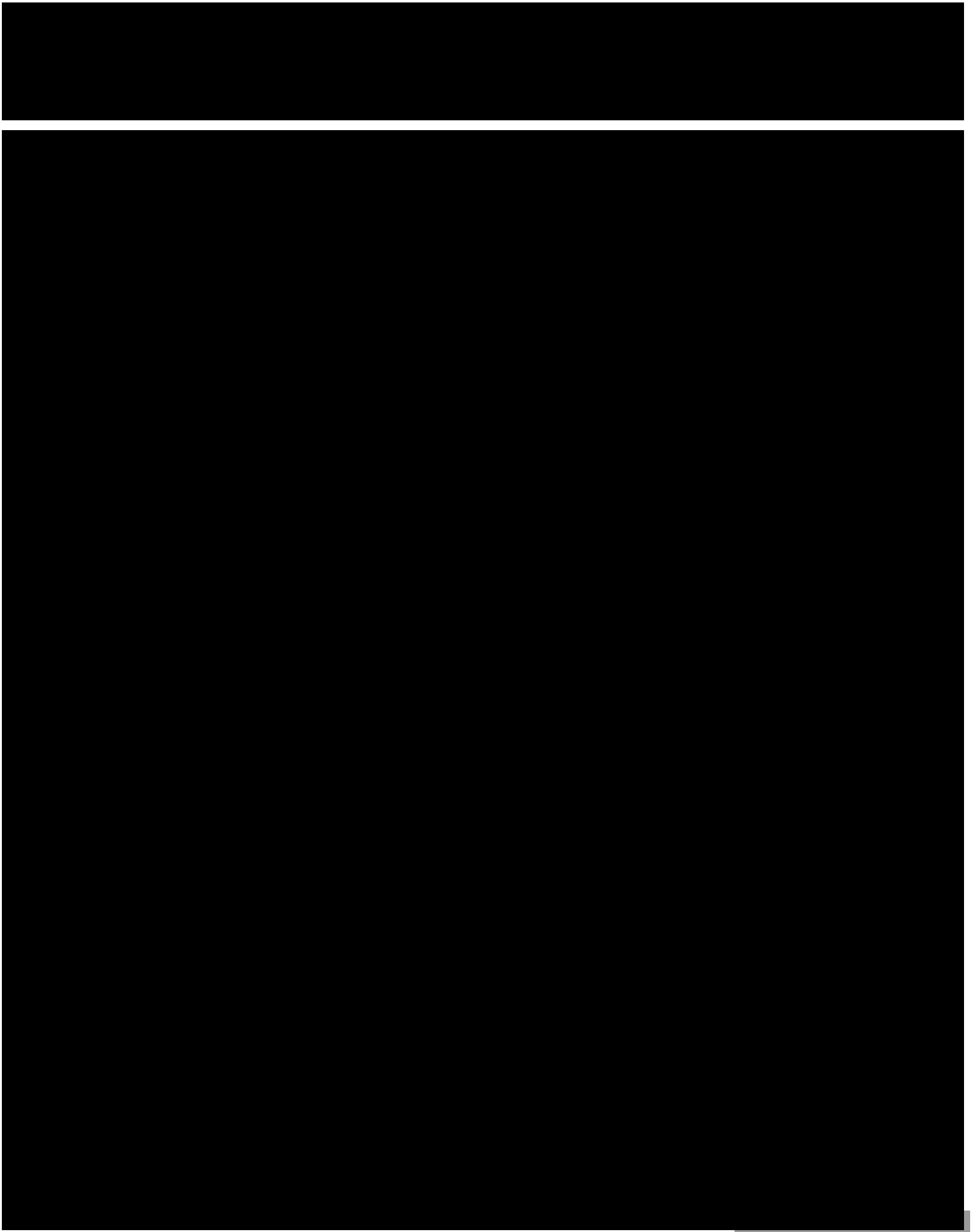

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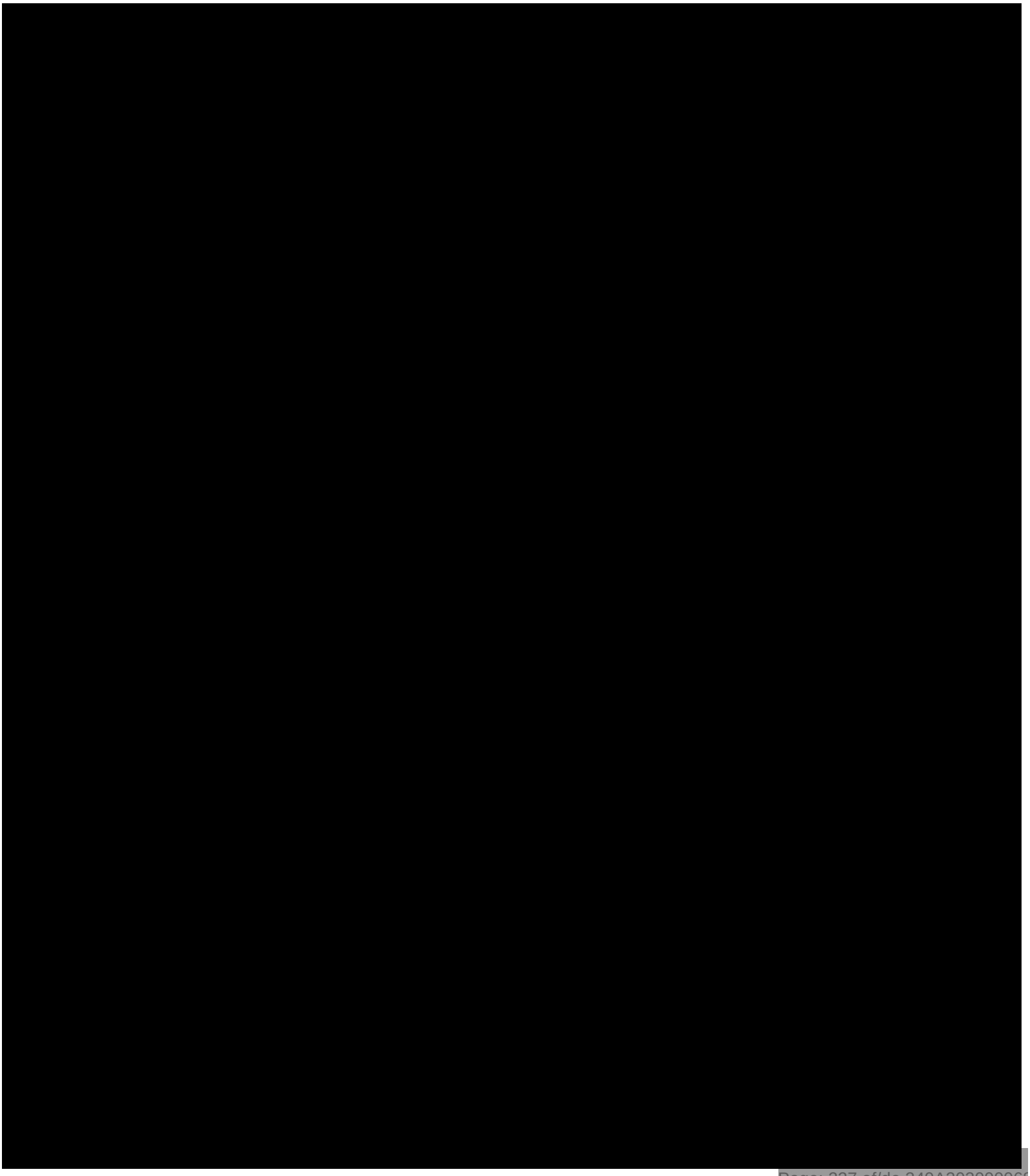

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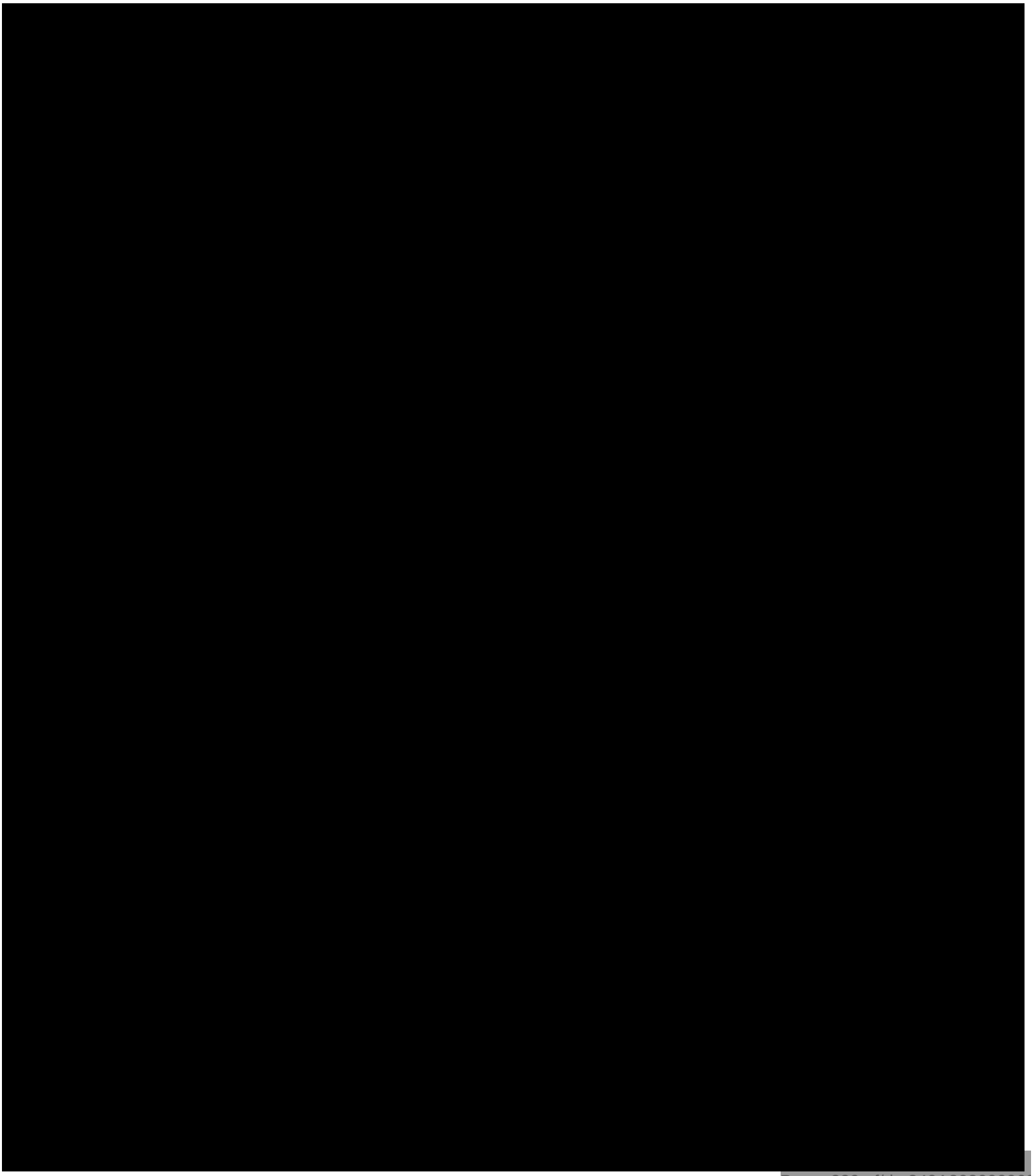

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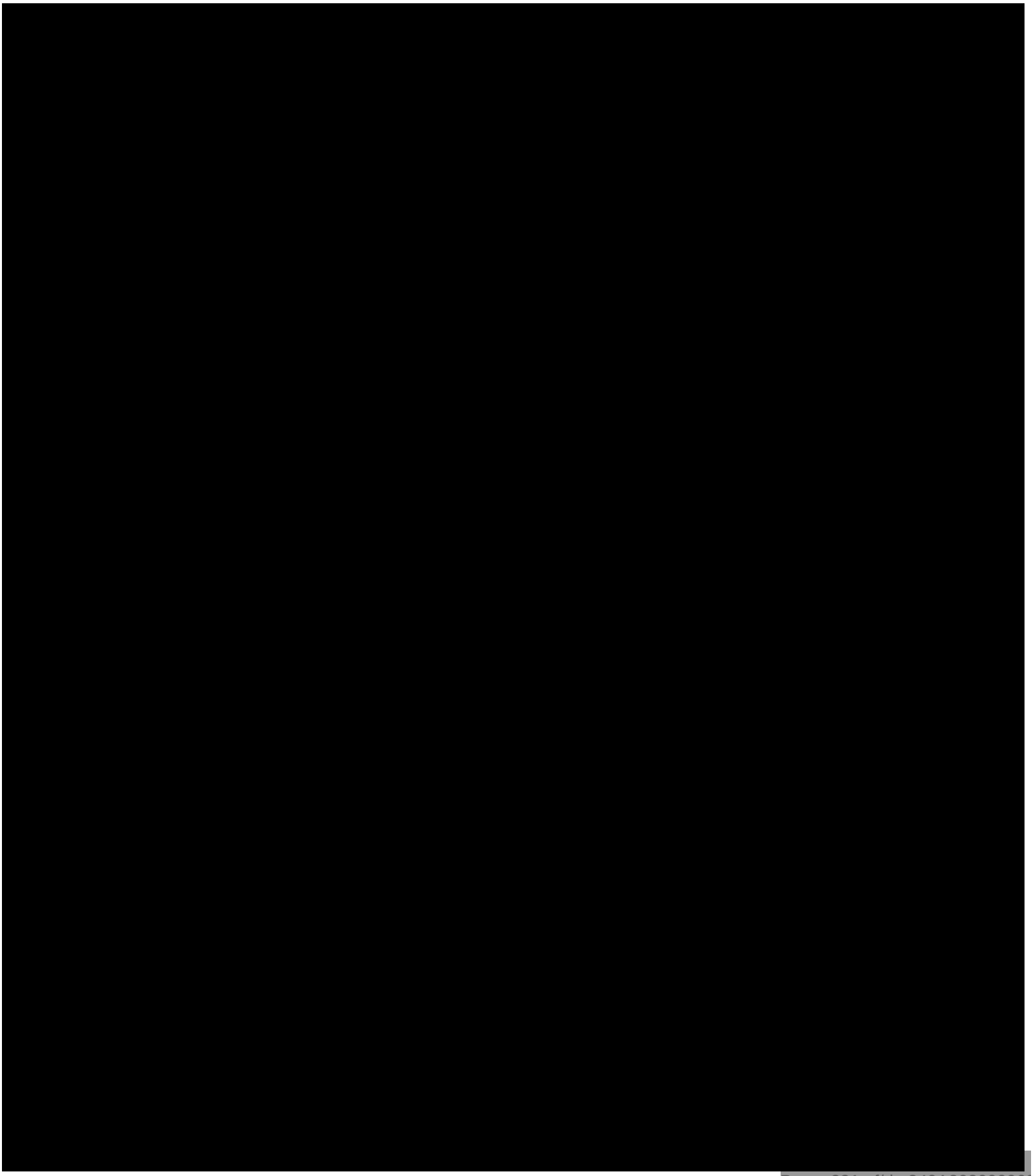

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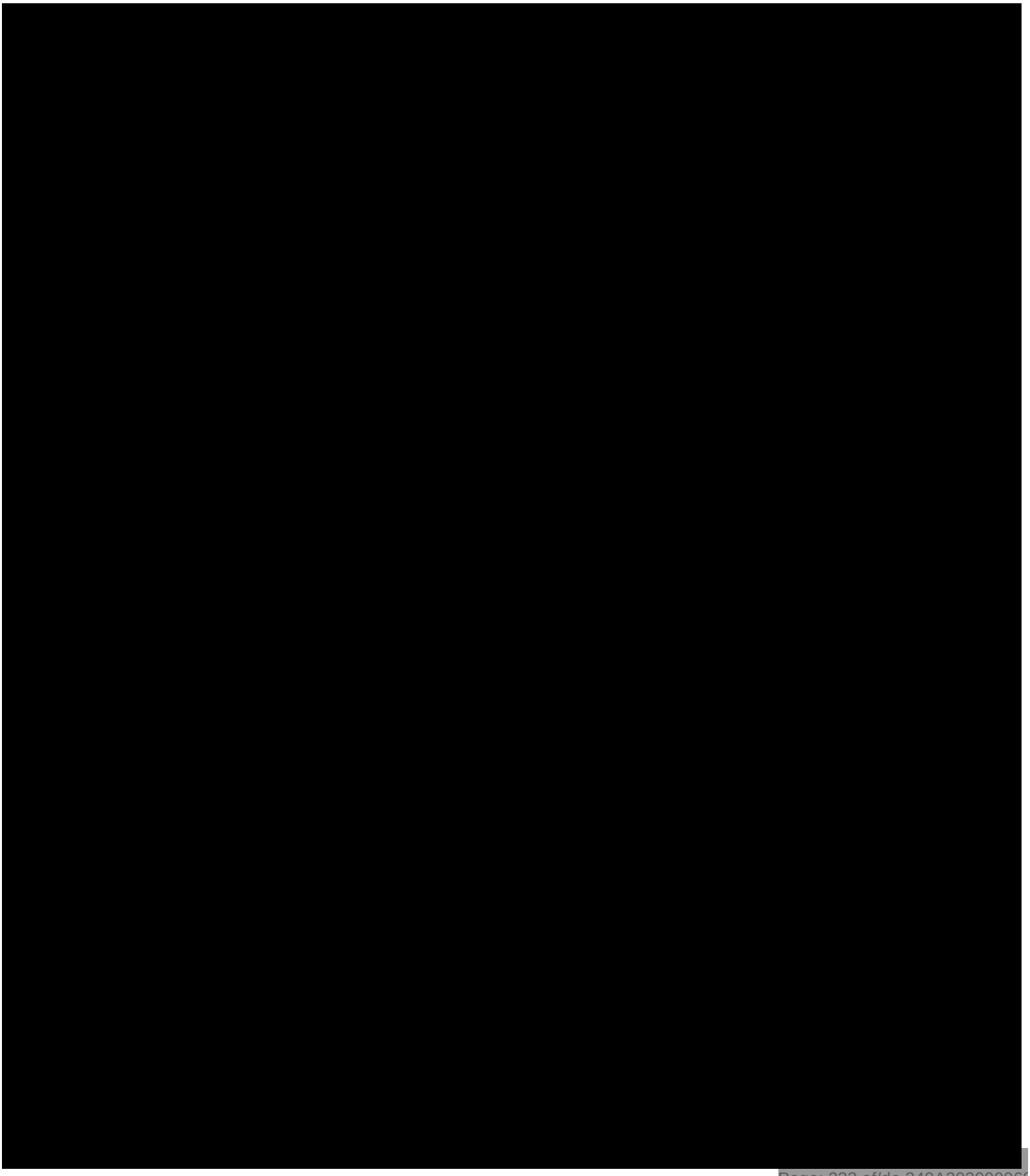

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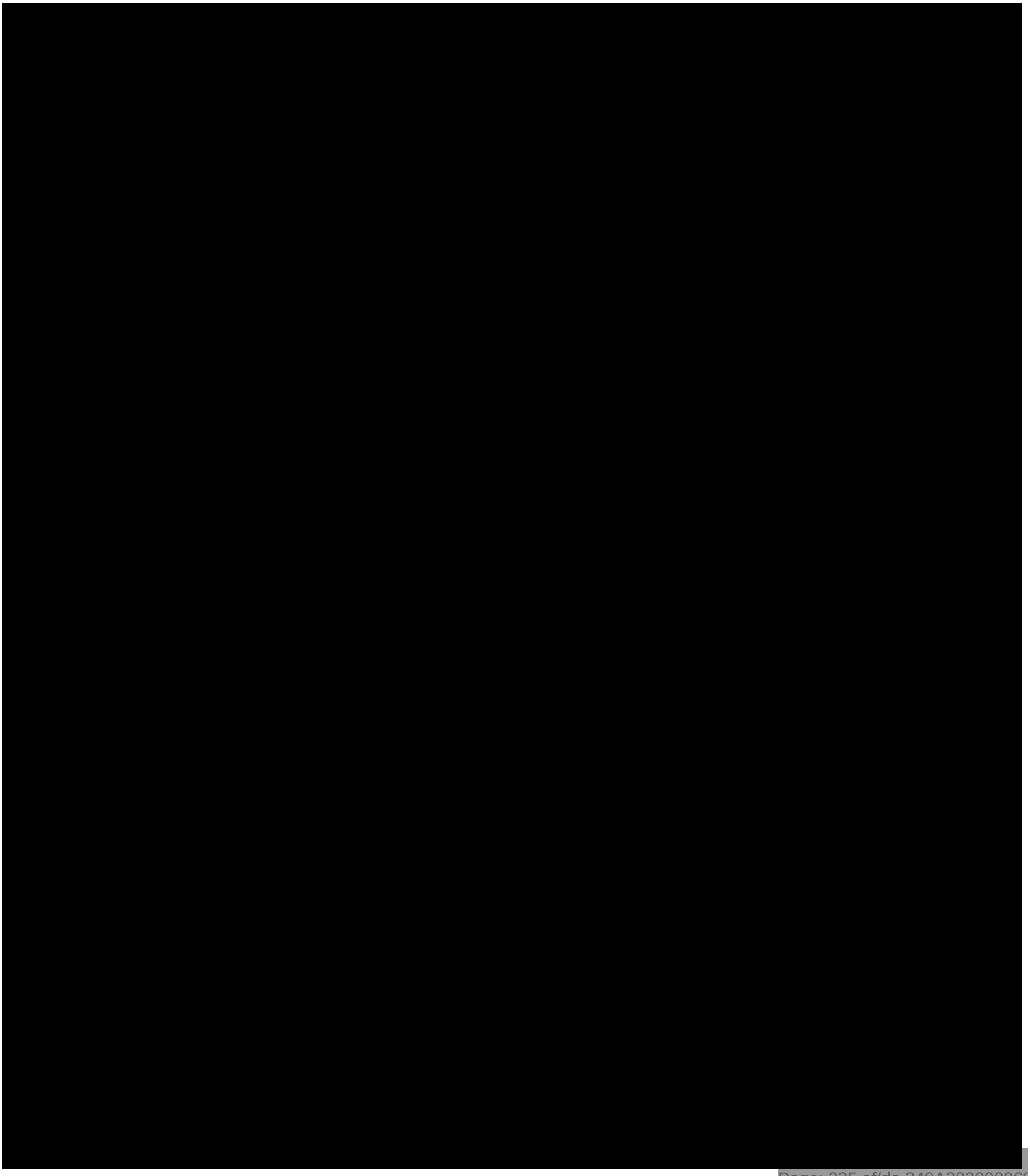

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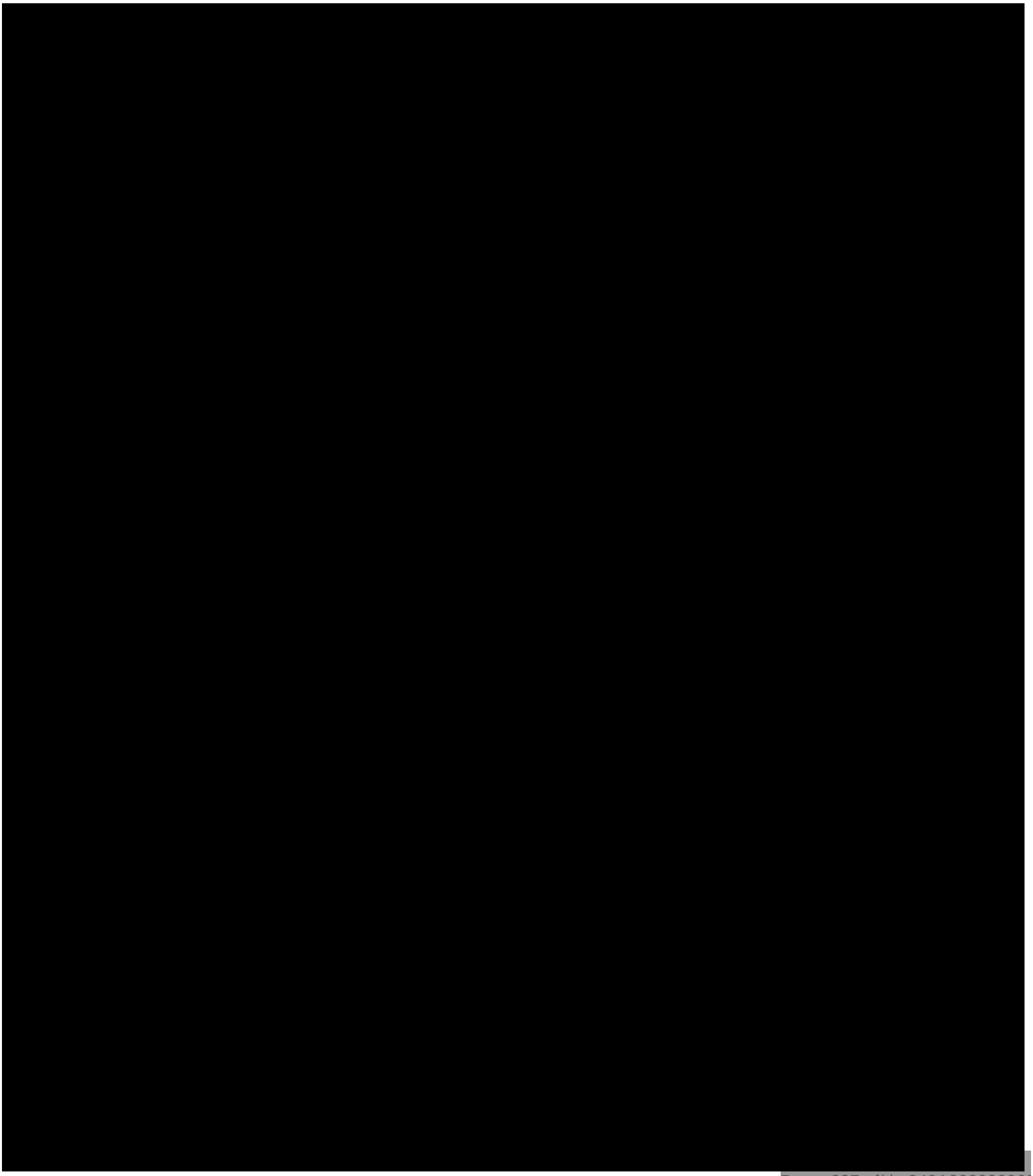

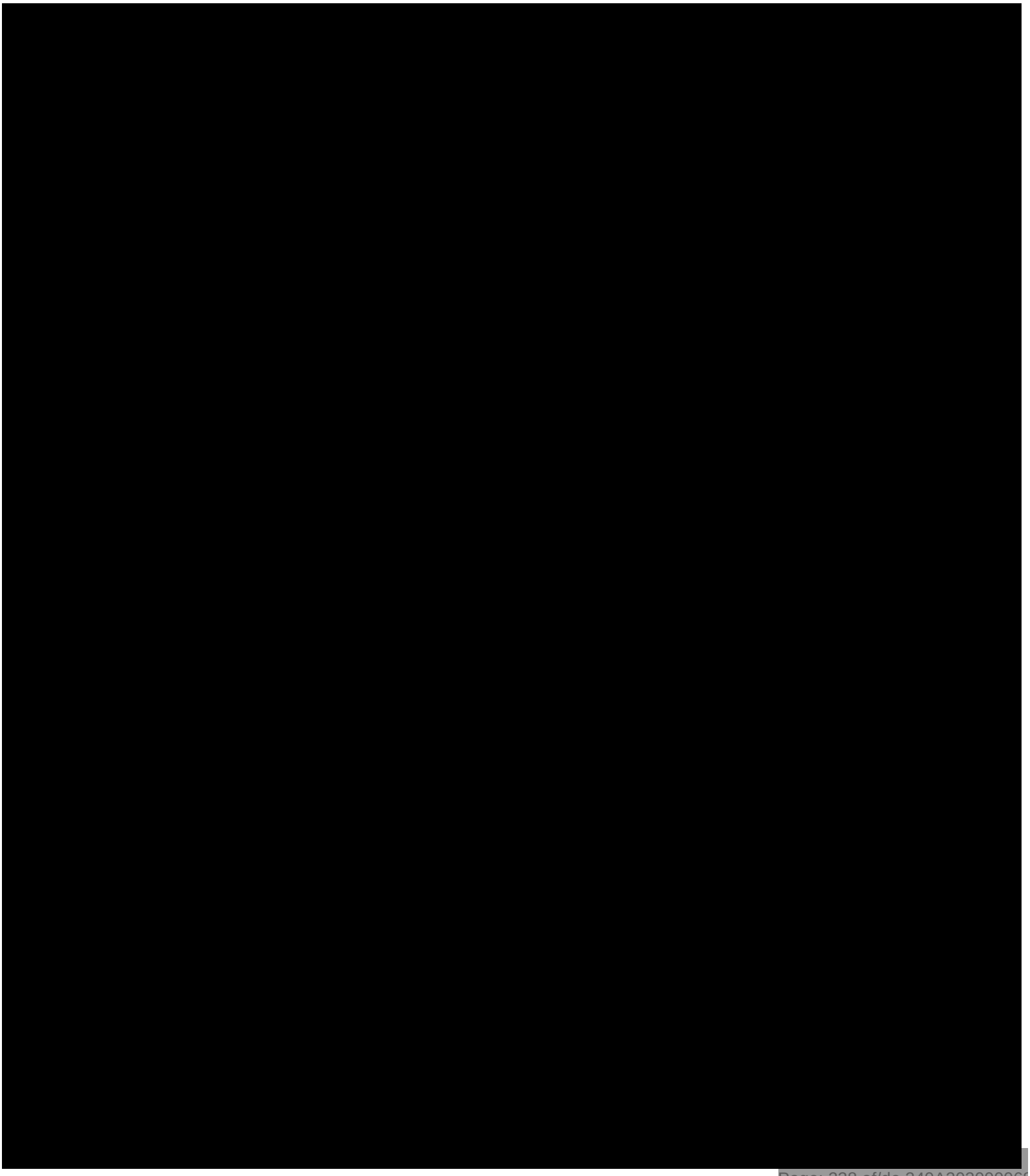

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