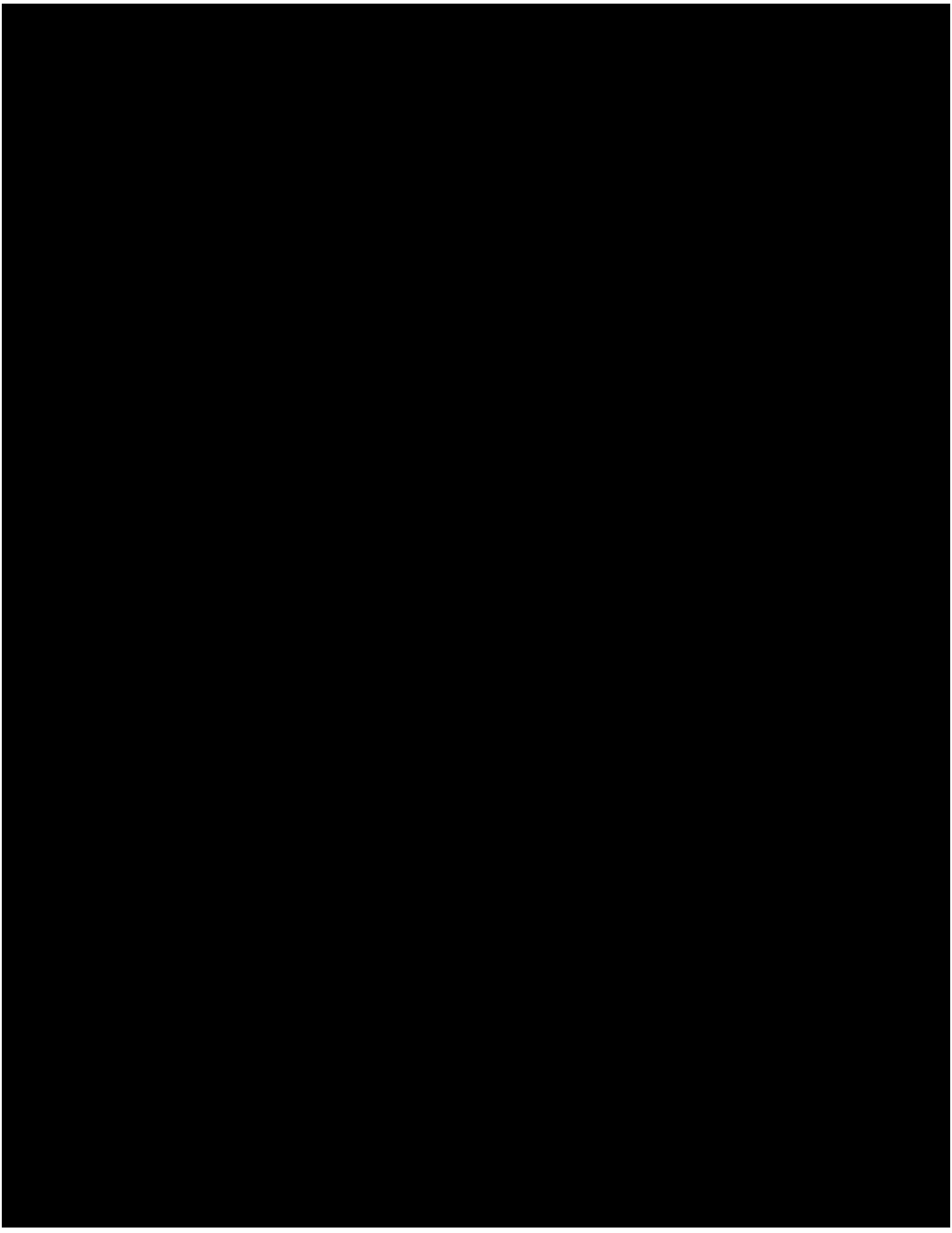
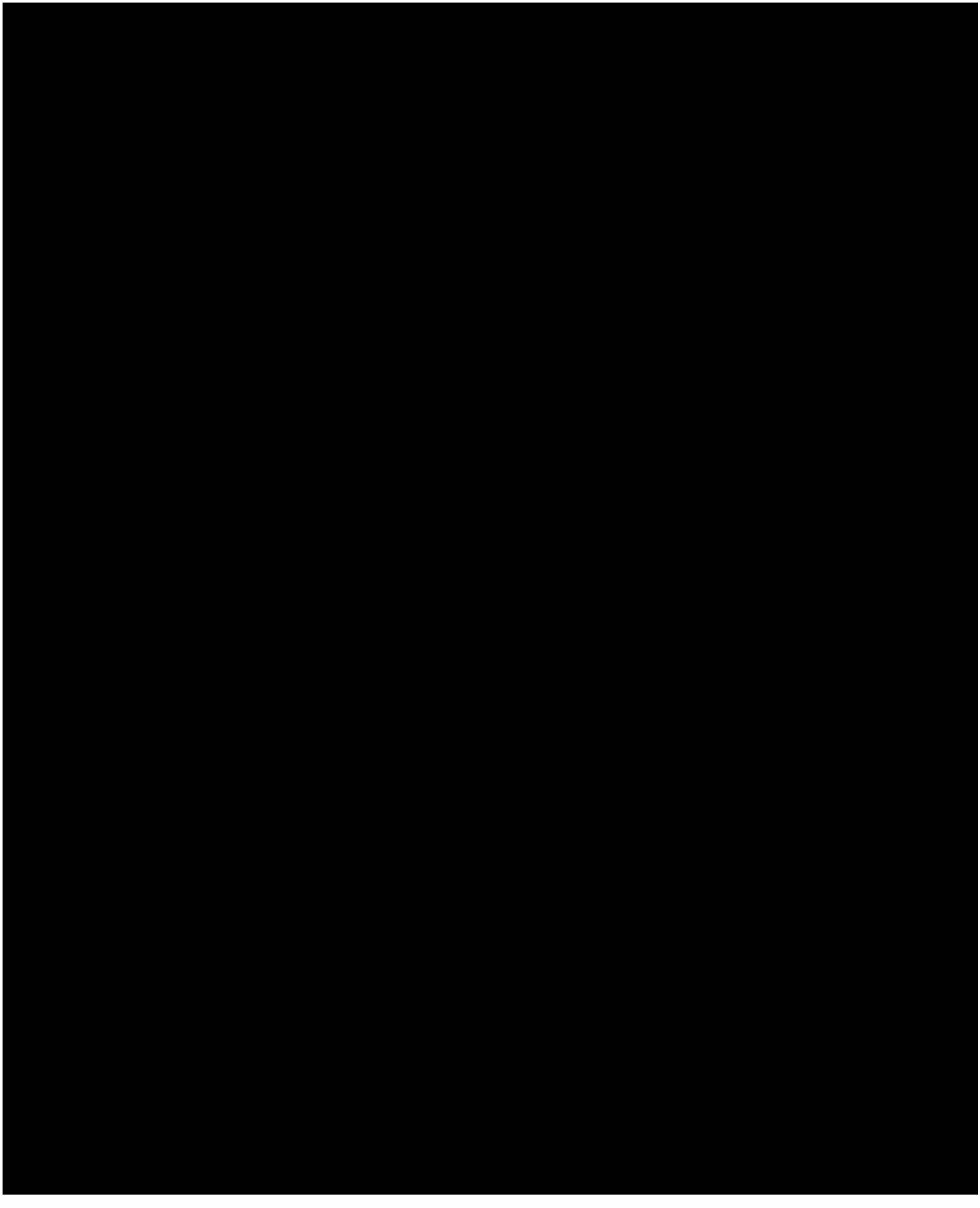
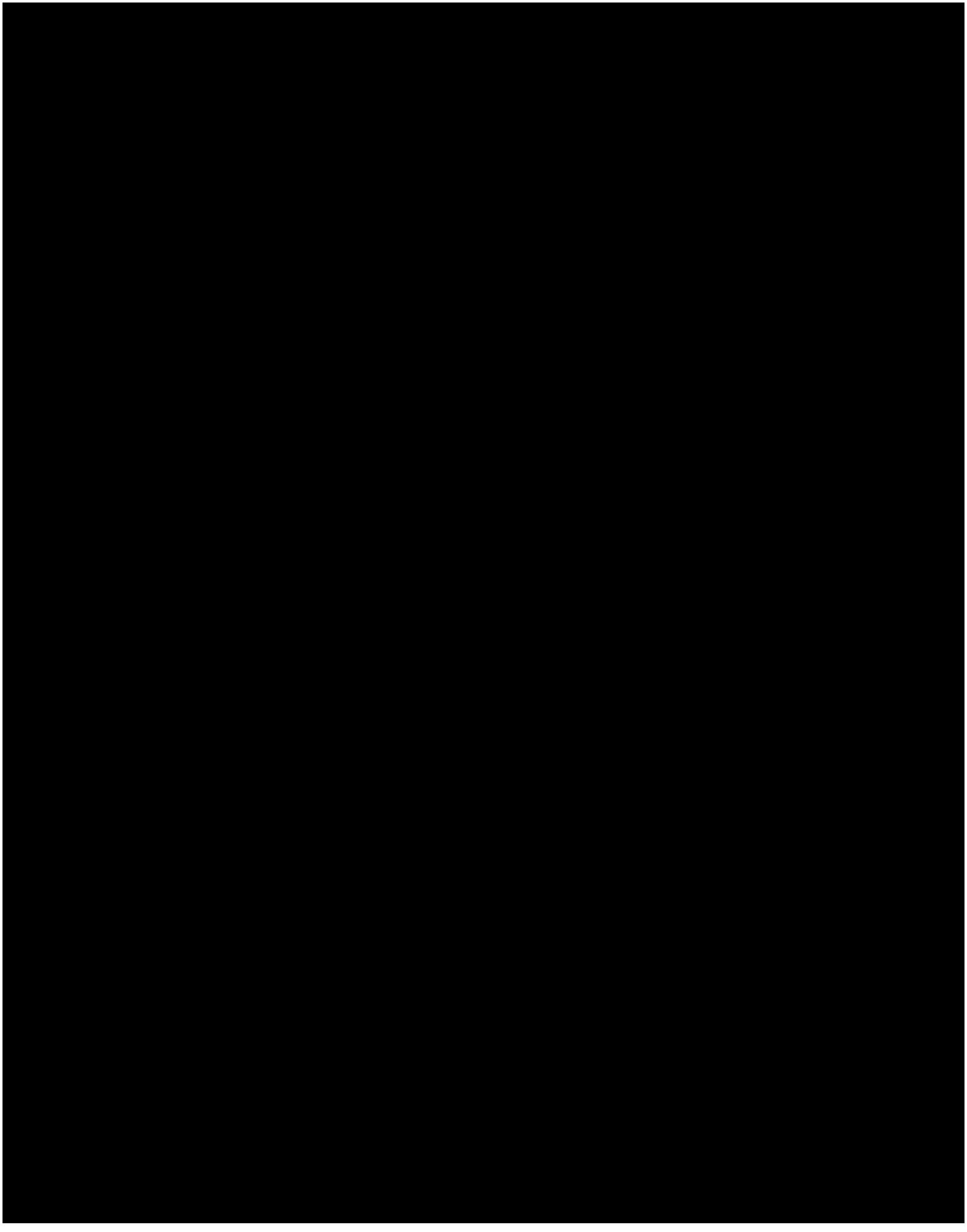
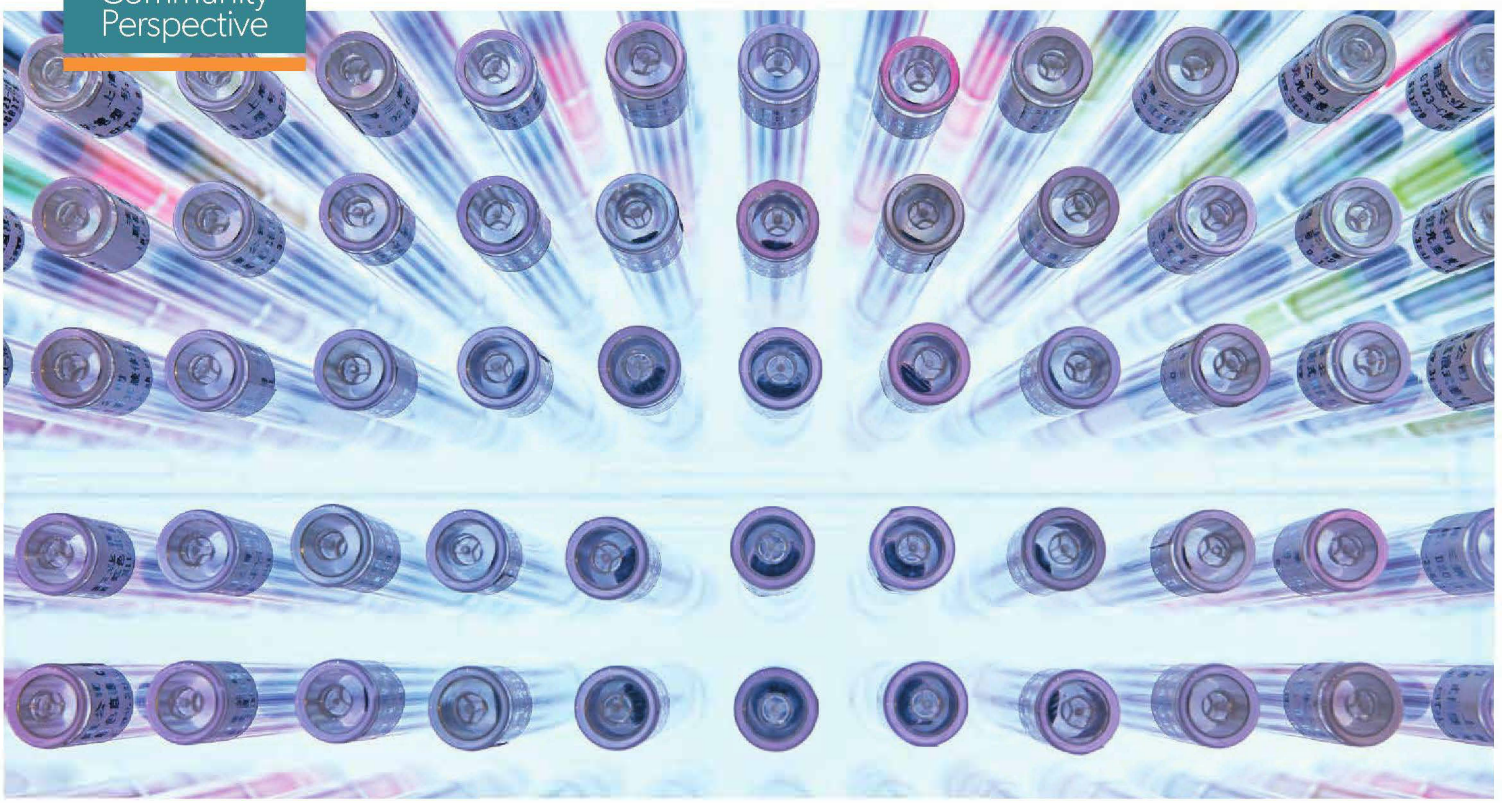








Advocating for Regulatory Approval to Improve Care for Patients With Dihydropyrimidine Dehydrogenase Deficiency

By Ken Surprenant, President, Advocates for Universal DPD/DPYD Testing

PRECISION MEDICINE plays two primary roles in healthcare: first, to point to safe and effective medicines for patients with a corresponding responder profile and, second, to identify medicines that cannot be metabolized or otherwise tolerated by patients. For instance, some individuals are unable to metabolize 5-fluorouracil (5-FU and its prodrug Xeloda), a drug that has a long history in cancer treatment.

Patients who are deficient in dihydropyrimidine dehydrogenase (DPD) cannot metabolize 5-FU, which results in buildup of the drug and often leads to severe adverse reactions or even death. DPD deficiency is defined as having low or no levels of the DPD enzyme and is typically associated with deleterious polymorphisms in the gene encoding DPD (DPYD). Such polymorphisms may lead to partial or complete deficiency (see **Inset**). Detecting DPYD variants is critical to avoid administering 5-FU treatment in DPD-deficient individuals and to instead prescribe an alternative therapy.

Though the risk of using 5-FU to treat DPD deficient patients has been known for more than 30 years, the groups responsible for cancer treatment guidelines and drug labels in the US have not recommended pre-screening (see also **Inset**).

The Advocates for Universal DPD/DPYD Testing (AUDT) came together as a group in 2021 following

the death of yet another loved one whose suffering could have been prevented with genetic testing prior to the start of treatment with fluoropyrimidine-based chemotherapy.[1,2]

The human cost of failing to test for DPD deficiency prior to administering 5-FU is the common experience that created, and sustains, the bond among these advocates. In addition to that common experience, the advocates also share a passion to help prevent others from suffering similarly, especially when the ability to avoid adverse outcomes is so easy to achieve.

Since joining together, we have been afforded more opportunities to share our stories and raise awareness among healthcare organizations. As a result, we gained the support of the Institute of Safe Medication Practices[3] and the National Community Oncology Dispensing Association.[4]

The increase in dialogue has also served to reveal more of the concerns that prevent those responsible for treatment guidelines and drug labels from recommending pre-screening and dose adjustments for DPD-deficient patients.

Progress towards improving the standard of care is noticeable, though far from concluded.

Starting down the advocacy path: First steps on a journey of 1,000 miles

In every case that pushed an AUDT member into advocacy, a friend or loved one was diagnosed with a form of cancer involving a solid tumor, typically gastrointestinal, breast, or head and neck cancer. Following the diagnosis, chemotherapy relying on a fluoropyrimidine, 5-FU or Xeloda (capecitabine), became part of the treatment plan.

Our understanding was that there was little risk of toxicity (see **Inset**) associated with the use of the drugs; after all, 5-FU has been used for more than 50 years to treat gastrointestinal cancer while capecitabine has been used for certain forms of breast cancer. Yet our friends and loved ones suffered following treatment, and most died within weeks of a single treatment, though a few suffered longer, often compounded with treatment delays, before dying.

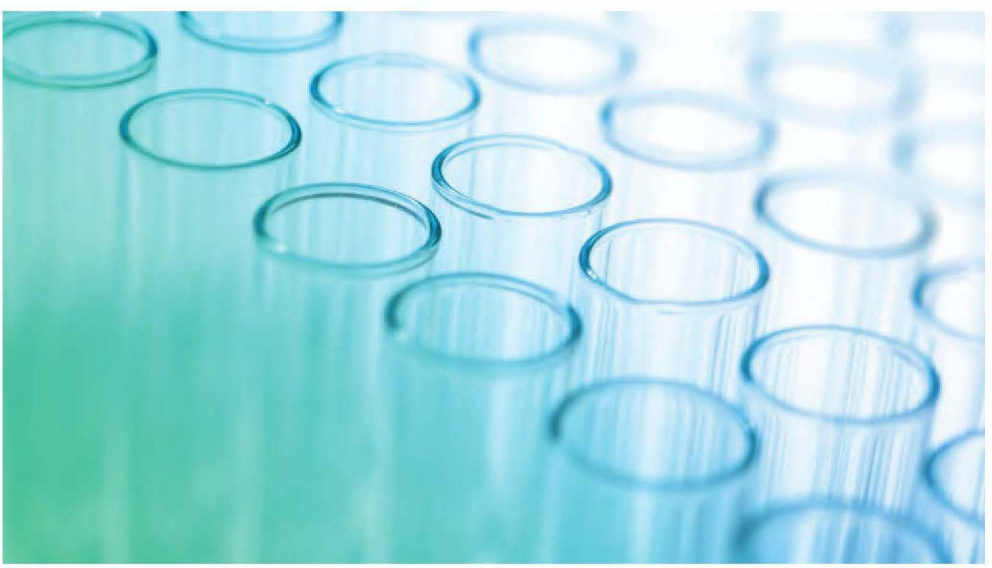
In our struggle to deal with our losses, we first sought to understand what happened and why. For 5-FU and Xeloda to work safely, a patient must have sufficient levels of DPD to reach and maintain a safe and effective therapeutic window following dosing. In brief, DPD serves to remove 5-FU from the body before it can damage healthy cells, but when DPD enzyme activity is compromised, the chemotherapy agents remain in the body longer, leading to severe toxicity and, in some cases, death.

Most patients are unaware if they are DPD deficient; they are asymptomatic and unless tested before the start of treatment, they will not know they are at a high risk of severe toxicity.

What has been done to raise awareness, change policy

Nearly 10 years ago, one of our advocates sought to raise awareness of the risk of DPD deficiency by creating a website.[5] Unfortunately, most people visited this site after experiencing a tragic outcome, not before. Nonetheless, the site has served to bring advocates together over time and to provide a means to share the stories of their loved ones' experiences.

As individual advocates, we tried in different ways to bring about an improved standard of care. For example, to support a young family whose mother tragically struggled with long-term suffering and care expenses, a community of friends created the StrongMom[6] website to support the family and to raise awareness of this health issue.



A few of us were afforded opportunities to share our stories. For example, the wife of one of our members shared her experience of how her toxic reaction resulted in halting her treatment. When she and her husband found a pharmacologist in France to phenotype her blood, she discovered she had partial DPD deficiency. While she found an oncologist willing to treat her at a reduced dose level and though she tolerated the adjusted dose of 5-FU chemotherapy, the treatment resumed too late to curb her cancer. Although her death was not reported as a toxic reaction, the delay cost her precious treatment time.

Meanwhile, in New York and New Jersey, individual advocates proposed legislation to require screening for DPD deficiency prior to the use of 5-FU. These bills stalled.

Our individual attempts to revise treatment guidelines have also included submitting multiple petitions to the National Comprehensive Cancer Network's (NCCN) Colorectal/Anal panel to update its guidelines to recommend pre-screening. To date, the NCCN has unanimously voted down each petition and treatment guidelines remain unchanged.

We have also attempted to revise drug labels to include a warning to 5-FU and Xeloda users of the issues with DPD deficiency. In 2014, one of our advocates submitted a petition through the US Food and Drug Administration's (FDA) citizen petition process, seeking changes to the drug labels to heighten awareness of the risk of DPD deficiency and to recommend pre-screening and dose adjustments for patients found to have partial deficiency.[7]

After two years of deliberation, the FDA responded in 2016.[7] The agency agreed to revise the drug labels' warnings and precautions to describe more clearly the risk of severe toxicity to DPD-deficient patients. In doing so, the labels no longer describe the risk of severe toxicity as "rare" or "unexpected." The FDA also agreed to add fatalities to the list of possible outcomes.

But the agency denied the recommendations to pre-screen patients and did not endorse dose reduction guidelines for patients with partial DPD deficiency, stating that these practices are not recommended by NCCN guidelines. The agency also questioned the predictive accuracy and reliability of genetic testing.

The FDA's response fell short of what we as advocates sought, but it served as a big first step for our efforts.

Impact in Canada, US court cases

While unsuccessful in the US, one of our members succeeded in bringing about

pre-screening in Quebec. After several years of tireless work, this widow saw the fruits of her labor when the province mandated pre-screening along with dose adjustment guidelines in 2019.[8]

Another widow brought a lawsuit against the US hospital where her husband died following adjuvant treatment with Xeloda. The parties settled out of court in 2022 with a payment to the grieving party and with a pledge to introduce staff training to address the risk of DPD deficiency.[9] Still, the hospital has not adopted pre-screening procedures, citing the absence of national treatment guidelines for testing. This settlement, however, has sent a signal to cancer centers of the potential liability of ignoring this important safety issue.

Encouraging road signs: Europe and elsewhere

Meanwhile, there has been heightened interest in DPD deficiency in peer-reviewed medical journals. A number of European teams published reports citing the cost effectiveness and the benefits to patients of using test results to guide treatment.[10,11,12] Indeed, some teams urged that the time had come to require pre-screening and dose guided treatment plans.[2,13]

France set the bar for improved outcomes in 2019 when it mandated testing for DPD phenotypes before the use of 5-FU or Xeloda. Within a year, the European Medicines Agency issued its recommendation to pre-screen patients using either DPYD genotyping or DPD phenotyping; it also recommended adjusting 5-FU or capecitabine dosage based on the level of DPD deficiency.[14]

Encouraged by these changes in Europe, we expected to see change in the US but that has not been the case so far. Despite the failure of US regulators to adopt these guidelines to date, we have seen an increased willingness among oncologists and pharmacologists to recognize the risk to DPD deficient patients.

The rallying point

Up until 2021, our individual advocacy activities took place in isolation. Then, Lindsay Murray, who had recently lost her mother due to DPD deficiency, reached out and compelled us to

DPD deficiency and avoiding drug toxicity

1. Fluorouracil (5-FU) and Xeloda are used to treat solid tumors typically found in gastrointestinal, breast, and head and neck cancer patients.
2. The DPD enzyme plays an essential role in removing the chemotherapy drug from the body before it can damage healthy cells. When DPD enzyme activity is diminished, severe toxicity is a highly likely outcome.
3. An estimated 10 percent to 40 percent of all patients suffer severe toxic reactions (grade >3) when treated with standard dosing[1,2,3] One notable US study, Alliance N0147, found 33 percent of patients receiving standard doses suffered severe toxicity.[4] The same study found DPD-deficient patients were at a significantly higher risk of adverse reactions: patients with partial DPD deficiency had a 50 percent to 88 percent risk of severe toxicity.
4. The death rate due to DPD deficiency in the US is controversial and not well documented but is estimated at 700 to 1,400 annually.[5]
5. Warning signs of early onset toxicity include severe forms of diarrhea, mucositis that inhibits drinking or eating, vomiting, peeling or blistering skin, and neutropenia.[6]
6. Genetic variants of the DPYD gene have been shown to lead to compromised DPD enzyme activity as first reported in 1988 by Robert Diasio, then at the University of Alabama and now of the Mayo Clinic.[7]
   - Four DPYD variants (c.1905+1G>A, c. 1679T>G, c.2846A>T, and c.1236G>A/HapB3) are associated with increased risk of severe toxicity for an estimated 5 percent to 7 percent of European descendants.[8,9]
   - Another deleterious variant, p.Y186C (rs115232898), has been discovered among an estimated 5 percent of African Americans.[10]
7. Tests are available to detect DPD deficiency and have been demonstrated to be life-saving and cost effective.[11,12,13] In most cases patients with DPD deficiency are asymptomatic prior to receiving 5-FU or Xeloda.[14]
8. Treatment guidelines, published by the National Comprehensive Cancer Network and the US Food and Drug Administration's drug labels have not required pre-screening.[15]

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Figure 1: Highlighting the human cost of ignoring DPD deficiency

join our efforts under an umbrella advocacy group. Her passion to bring about an improved standard of care, to honor the loss of her mother, and to help others avoid that suffering was the rallying cry for us.

We organized as a group loosely that year and worked to bring our voices together in two ways: first, we established a new website;[15] and then collaborated with the American Society of Pharmacovigilance (ASP) to share a booth at the American Society of Clinical Oncology's Quality Care Symposium in Boston in September of that year. There we attempted to highlight the human cost of ignoring DPD deficiency (see **Figure 1**) with our stories available online.[16]

Then with encouragement from medical professionals who shared our interest in changing the standard of care, we formed officially as a 501(c)3 non-profit organization in 2022.

Picking up the pace

When we formed AUDT, we hoped that by joining our voices together we would have a larger impact. Since its founding, we have certainly been given more opportunities to present our case. Thanks to our medical advisors and to other supporters, including ASP and the GI Cancer Alliance, we have had opportunities to share our stories in different virtual forums and garner increased support.

As a result, the Institute for Safe Medication Practices came out to support pre-screening and dose adjustment in its July 2021 newsletter[17] and the National Community Oncology Dispensing Association published in December 2021 a recommendation for DPYD testing prior to fluoropyrimidine treatment.[18] We contributed to a workshop on the need and benefit of pre-screening for DPD deficiency for the Hematology Oncology Pharmacy Association's continuing education program and we had news coverage of our efforts.

We learn more as we go along. One of the lessons we learned came as a result of the ISMP newsletter. The co-chairs of the NCCN Colorectal/Anal Cancer panel responded by expressing their concern that reducing doses in response to DPD deficiency may reduce the chance to treat patients effectively.[18] Subsequently, one of our medical advisors, Daniel Hertz from the University of Michigan College of Pharmacy, reported in the *Journal of Clinical Oncology* that there is "no direct evidence of efficacy reduction."[20]

While the NCCN has not budged, the FDA edged forward in 2022 in response to another citizen petition. This petition, submitted in 2020 with the support of four experts – oncologists and pharmacologists – cited the new practices in Europe, among other compelling reasons, for the agency to reconsider its stance. The petition made the case that testing is a much safer route than not. The petition also noted that once the FDA approves testing, the market will respond with even better testing capabilities. The petition also recommended, as the previous one did, to use test results to guide chemotherapy dosing levels for DPD-deficient patients as well as to encourage physicians to discuss the risk of DPD deficiency with patients and to offer them testing.[21]

The FDA responded only to the recommendations pertaining to Xeloda while the 5-FU drug label remains under review as part of the FDA's Project Renewal.[21] The FDA agreed to revise the warnings and precautions section of the Xeloda drug label to make discussion of DPD deficiency more prominent and have it ask physicians to "consider testing for genetic variants of DPYD prior to initiating Xeloda to reduce the risk of serious adverse reactions if the patient's clinical status permits." The FDA label goes on to warn that serious adverse reactions may still occur and that current tests may vary in accuracy.

The agency also approved revisions to the patient counseling section of the label, including moving it higher in the order of topics discussed and adding that physicians should "inform patients of the potential for serious and life-threatening adverse reactions due to DPD deficiency and discuss with your patient whether

they should be tested for genetic variants of DPYD." It further addressed the risk of DPD deficiency in the patient information section and the drug label's new pharmacogenomics section.

The FDA, however, did not recommend universal testing prior to prescribing these drug treatments. The agency raised questions and concerns about test reliability and accuracy, the inapplicability of testing to the general US population, and stated that "most known DPYD variants associated with decreased DPD activity are reported to be of low frequency." It further added that there was "insufficient evidence … regarding the relative benefits and risks of existing testing approaches" as well as the possible detriment to a patient's cure if treatment is withheld or insufficiently adjusted.

We applaud this progress, but it again comes short of our goal of universally requiring pre-treatment screening for DPD deficiency. Though the FDA now encourages physicians to discuss and consider testing, this leaves patients to deal with many oncologists who may point to the absence of NCCN guidelines as reasons to dismiss the need for testing. To help patients navigate along their journey of seeking treatment, we have published what we have found as Clinical Laboratory Improvement Amendments-certified laboratories that offer DPYD tests.[22]

There is also little guidance for physicians who receive test results. The FDA has not come out in support of dose adjustment for patients with partial deficiency despite the presence of guidelines published and maintained by the Clinical Pharmacogenomics Implementation Consortium.[23]

While the FDA and NCCN do not recommend pre-screening and dose management, we have found a number of US institutes and practitioners who are implementing some form of DPD deficiency pre-screening as part of their practice.[24] An early leader in testing, Dartmouth Cancer Center's Gabriel Brooks saw the tragic effects of 5-FU toxicity during his fellowship and has implemented pre-screening in his practice for treating GI cancer patients; he serves as another of our group's medical advisors. Brooks and other clinical leaders offer hope that the NCCN and FDA will soon update their positions.

Perhaps the single largest breakthrough in creating test leaders is a direct result of the efforts of our team's vice president. Murray, whose passion for change led us to form AUDT, succeeded in bringing about change at the cancer institute that treated her mother. Starting in 2021, she worked with a team at the Dana Farber Cancer Institute (DFCI) in Boston to initiate and implement DPD deficiency pre-screening.[25] Effective since December 2022, DFCI pre-screens patients unless they "opt out." Processes were put in place to ensure patients with DPD deficiency are identified and then treated accordingly, such as with dose adjustment. This response at DFCI demonstrates that once there is agreement upon addressing the problem of patient safety, procedural change is not insurmountable. DFCI's leadership, along with the other test leaders, gives us hope that other leading cancer centers will follow and ultimately prompt the NCCN and FDA to embrace the need for pre-screening and dose management.

The journey continues

We have seen progress towards improving the standard of care in the US, however, we have not concluded our journey. Since the time of our first advocacy steps, too many patients have died from standard dose chemotherapy treatment of DPD deficient patients. Estimates place the US death toll from DPD deficiency at more than 700 deaths per year.[26]

If you too see the current standard of care as inadequate to ensure safe treatment with 5-FU, please consider joining in our advocacy efforts. Only when prescreening and dose management is adopted across the US will we be able to rest our advocacy efforts. PMQ

Ken Surprenant

President, Advocates for Universal DPD/DPYD Testing

Ken has advocated for improved treatment guidelines for DPD deficient patients following the loss of his first wife, Kathryn, due to a toxic reaction to 5-FU chemotherapy in 2012. He is a founding member of Advocates for Universal DPD/DPYD Testing (AUDT), a group of patient advocates and medical advisors who seek to improve the standard of care for DPD deficient patients with pre-treatment screening and dose adjustment. With the help of many contributors, Ken's citizen petitions led the US Food and Drug Administration to update drug product labels (2016 and 2022) to more clearly identify the risk of severe toxicity for DPD deficient patients. Ken served over 40 years in federal service, managing multiple program managers and staff responsible for the development and operations of logistics information systems. He enjoys traveling, projects, and activities with his new wife, Elizabeth, and his children and grandchildren.

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DPYD Testing: Time to Put Patient Safety First

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In 2018, a patient received capecitabine without prior testing for dihydropyrimidine dehydrogenase (*DPYD*) and later presented with vomiting, rash, and diarrhea. The hospital failed to provide uridine triacetate in a timely fashion, and the patient died. The patient's widow filed a wrongful death lawsuit against Oregon Health Sciences University (OHSU) and assisted in the formation of a nonprofit organization to advocate for *DPYD* testing for fluoropyrimidines. A settlement for $1 million US dollars was reached requiring OHSU oncologists to undergo education about *DPYD* testing and inform their patients about its availability.[1] Clinical practice guidelines from the National Comprehensive Cancer Network (NCCN) and ASCO still do not support testing for *DPYD* genetic variants before fluoropyrimidine chemotherapy. The US Food and Drug Administration (FDA) package inserts for capecitabine and fluorouracil (FU) acknowledge patients with dihydropyrimidine dehydrogenase protein (DPD) deficiency have increased risk of life-threatening toxicity; however, instead of recommending preemptive testing, they posit an unlikely scenario in which patients who have known DPD deficiency should discuss it with their physicians.[2,3] The European Medicines Agency, the French National Agency for the Safety of Medicines and Health Products, and the Medicines and Healthcare products Regulatory Agency have each approved guidelines for preemptive *DPYD* testing for patients treated with fluoropyrimidines.[4]

Like all genetic tests, levels of evidence vary for each allele, but sufficient data are now published in the literature to conclude that individuals harboring certain *DPYD* variants are at increased risk of toxicity or death when administered standard doses of fluoropyrimidines. The genetic basis for the association between slow FU metabolism, pharmacokinetics, and toxicity was established in 1988.[5,6] In 1990, DPD activity was associated with FU plasma concentrations.[7] *DPYD*2A*, exon skipping IVS14G>A variant (c.1905+1G>A, rs3918290), was identified in 1995 and associated with FU toxicity in 1996.[8,9] A large number of studies are now published establishing the relationship between *DPYD* variants and fluoropyrimidine pharmacokinetics.[10] This commentary will establish that pretreatment *DPYD* testing is well justified and recommend dose reduction in those patients with a decreased function variant. We recommend an immediate modification to the oncology treatment guidelines that include a fluoropyrimidine.

Severe Fluoropyrimidine-Associated Toxicity

A recent meta-analysis of 13,929 patients in 35 studies found that patients carrying *DPYD*2A* were much more likely to experience severe life-threatening toxicity from fluoropyrimidine therapy than those carrying only wild-type alleles.[11] The NCCN colon cancer guideline discusses some of these studies, and we agree with the view presented therein: "Pretreatment *DPYD* testing of all patients has the potential to identify the estimated 1%-2% of the population with truncating alleles that may herald an increased risk of severe toxicity." However, the NCCN statement is not broad enough: Other *DPYD* variants have sufficient levels of evidence to justify testing (eg, c.1679T>G, rs55886062, *DPYD*13*; c.1129-5923C>G, rs75017182, *DPYD HapB3*; and c.2846A>T, rs67376798, p.D949V), raising the number of at-risk patients to approximately 9% of the US population.[10] Table 1 shows the recommended initial dose based on *DPYD* genotype-predicted phenotype.[10]

Fluoropyrimidine Efficacy

A prospective *DPYD* genotype-guided dose reduction (53% dose intensity) study resulted in similar efficacy in 40 *DPYD*2A* carriers versus matched controls.[12] Retrospective studies involving standard dosing found no relationship between *DPYD* SNPs and progression-free survival or overall survival in spite of a 50% dose reduction in *DPYD*2A* carriers.[13] Seven more clinical studies examining *DPYD* polymorphisms with a dose reduction did not observe a difference in response, time to progression, progression-free survival, and/or overall survival.[14] We were unable to find a study demonstrating a decrease in efficacy in patients with *DPYD* variants who were treated with a reduced dose. Thus, there is no evidence that a priori dose

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TABLE 1. Initial Dose Recommendations

DPD Activity Score[a]	% of Standard Fluoropyrimidine Dose[a]
2.0	100
1.5	50
1.0	50
0.5	< 25% if avoiding therapy unsuitable[b]
0.0	Avoid

Abbreviation: AS, activity score.

[a]DPD phenotype is based on activity score, which is a score developed from variants in the *DPYD* gene. A score of 2 represents an individual carrying two normal function alleles. A score of 1 or 1.5 represents an intermediate metabolizer carrying one normal function allele and one allele with decreased function (AS = 1.5) or absent function (AS = 1.0). A score of 0-0.5 represents a poor metabolizer carrying one no function allele and one allele with decreased function (AS = 0.5) or absent function (AS = 0).

[b]Clinical Pharmacogenetics Implementation Consortium guidelines also recommends use of phenotyping tests and therapeutic drug monitoring.

adjustments for *DPYD* carriers decreases fluoropyrimidine efficacy, and low-activity variant carriers treated with standard of care appear to have similar efficacy once an acceptable dose is found.

Pharmacokinetic Considerations

One study prospectively recruited heterozygous *DPYD*2A* carriers (n = 8) and wild-type carriers (n = 5) and demonstrated a significant difference in terminal half-life ($T_{1/2}$) between the two groups for single FU doses of 300 and 450 mg/m^2 (mean $T_{1/2}$ was 60% longer for those with a variant).[15] A larger study found a statistically significant 1.5-fold and 1.3-fold higher area under the concentration versus time curve (AUC) in patients with a *DPYD*2A* variant receiving a single FU dose of 300 mg/m^2 and 450 mg/m^2, respectively.[16] The mean FU clearance of *DPYD*2A* heterozygotes was 53% for controls.[17] Two case reports are published in which a heterozygous *DPYD*2A* carrier had a 2.5-fold higher $AUC_{0\text{-}3\ hours}$ and another had 66% lower FU clearance normalized for bioavailability than control patients.[18,19] Two genotype-guided dosing studies found no difference in the AUCs of *DPYD*2A* variant carriers receiving reduced doses compared with wild-type control patients receiving standard doses.[20,21] Thus, *DPYD*2A* carriers have greater exposure when provided standard dosing, and adjusting fluoropyrimidine dose on the basis of *DPYD*2A* genotype normalizes exposure across genotypic groups.

Practical Basis for a Study Involving Randomized Genotype-Guided Dosing

Although randomized clinical trial evidence is the gold standard for justifying clinical validity and clinical utility of genetic testing, obtaining such evidence is highly impractical, potentially delaying testing implementation for several years.

An ideal study design to prospectively validate *DPYD* genotyping before fluoropyrimidine administration would randomly assign a cohort to receive standard therapy despite a *DPYD*2A*, *DPYD*13*, *HapB3*, and *D949V* genotypes, which presents ethical and legal concerns because physicians may be obligated to act on this information to avoid severe toxicity in their patients. Another design could randomly assign patients to a nongenotyped cohort versus a genotyped cohort, with the genotyped cohort then receiving treatment with standard or reduced fluoropyrimidine dosing depending on genotype. Such a study likely would suffer from difficulty recruiting. Given these constraints, it is doubtful whether a randomized genotype-directed study will ever be conducted.

NCCN board members acknowledge the question of whether genotype testing should be implemented as standard of care is probably impossible to answer with traditional randomized studies, and they suggest a real-world study would be sufficient.[22] Yet, real-world studies published for the past 27 years in the scientific literature consistently demonstrate the relationship between *DPYD* variant carriers and toxicity. The NCCN and ASCO guidelines should act on these data to mitigate the incidence of ongoing life-threatening toxicity in the United States.[11]

Position of the Group

The NCCN guideline for the treatment of colon cancer (Table 2) states that *DPYD* variant carriers have significant risk of life-threatening toxicity and that *DPYD* testing is a cost-effective method to reduce such toxicity. NCCN's primary objection to testing DPD activity involves uncertainty that every patient with low DPD activity is at risk and the degree to which *DPYD* variants confer such risk. In public commentary, NCCN board members state further studies are required to mitigate the possibility that dose reduction would reduce fluoropyrimidine efficacy in some patients.[22] Current evidence suggests that dose adjustments do not alter efficacy; thus, a requirement for additional efficacy research should not supersede established concerns of unacceptable rates of life-threatening toxicity in *DPYD* low-activity variant carriers because the practice of medicine is guided by primum non nocere.

Risk/benefit analysis includes integrating evidence and uncertainties within the context of unmet needs.[23] Similar to most laboratory tests, *DPYD* testing has never been expected to provide certainty that a patient will develop drug toxicity; however, it does indicate a higher risk for severe or life-threatening toxicity that should be considered before treatment. The NCCN colorectal cancer guideline stipulates to the risk of life-threatening toxicity and then goes on to ignore it because "… it is not certain that every one of these patients is at risk." If one were to demand 100% predictive value for every test involving selection of an appropriate cancer treatment, almost no individual test would meet this standard for use in clinical care. Other tumor type NCCN

TABLE 2. NCCN Guideline for *DPYD* Testing (version 1.2022—February 25, 2022)

"Dihydropyrimidine dehydrogenase is the enzyme that catabolizes fluoropyrimidines. Individuals with certain variants of the dihydropyrimidine dehydrogenase gene, *DPYD*, have a significantly elevated risk for severe, life-threatening toxicity after a standard dose of fluoropyrimidine because these variants result in a truncated protein and prolonged systemic exposure to fluoropyrimidine. Pretreatment *DPYD* testing of all patients has the potential to identify the estimated 1%-2% of the population with truncating alleles that may herald an increased risk of severe toxicity. These patients could receive dose reductions or could be offered nonfluoropyrimidine regimens, although it is not certain that every one of these patients is at risk. Two prospective studies have shown *DPYD* genotyping and fluoropyrimidine dose individualization to be feasible in clinical practice, improve patient safety, and be cost effective. In a prospective study, 22 patients with the *DPYD*2A* variant allele (of 2,038 patients screened; 1.1%) were given a fluoropyrimidine dose reduction of 17%-91% (median, 48%). Results showed a significant reduction in the risk of grade ≥ 3 toxicity compared with historic controls (28% *v* 73%; $P < .001$). None of the patients died from drug toxicity, compared with a 10% death rate in the historical control group. Another prospective study identified 85 patients with any of the four *DPYD* variant alleles (8% of 1,103 patients screened) who received an initial fluoropyrimidine dose reduction of either 25% or 50% depending on the specific allele. This study reported that the RR of severe fluoropyrimidine-related toxicity was reduced for genotype-guided dosing for all studied alleles compared with the historical cohorts. However, because fluoropyrimidines are a pillar of therapy in CRC and it is not known with certainty that given *DYPD* variants are necessarily associated with this risk, universal pretreatment *DPYD* genotyping remains controversial, and the NCCN Panel does not support it at this time."[38]

Abbreviations: CRC, colorectal cancer; NCCN, National Comprehensive Cancer Network; RR, relative risk.

guidelines that use fluoropyrimidines as a treatment option fail to mention *DPYD*.

Evidence demonstrates that standard doses of FU and capecitabine are intolerable for most *DPYD*2A* carriers anyway.[13,17,24-26] Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for dosing fluoropyrimidines in DPD intermediate or poor metabolizers explicitly recommend dose escalation as tolerated.[10] We, therefore, believe *DPYD* genotyping should be recommended in the NCCN and ASCO guidelines for any patient diagnosed with cancer in which fluoropyrimidines are administered, provided testing does not interfere with clinical scenarios in which it does not add value (eg, the patient already tolerated a specific dose) or testing delays urgently needed therapy (eg, test results are available in 3-10 days).

Modification of these guidelines must be addressed immediately. OHSU originally denied fault in the wrongful death suit, justifying this claim by referring to national expert consensus.[1] OHSU is clearly relying on guidelines set forth by NCCN and ASCO. Although the NCCN stance against routine *DPYD* genotyping may have been acceptable in the past, accumulating data regarding the strong association of *DPYD* gene variants with severe toxicity make that stance increasingly untenable and possibly leaves cancer centers vulnerable to claims of malpractice in cases of fatal toxicity. On the basis of a survey of 18.2% of US medical oncologists, *DPYD* testing is limited by a lack of guidelines or recommendations for dosing decisions,[27] although some institutions are launching *DPYD* testing programs to avoid fluoropyrimidine toxicity.[22] Updating the guidelines to promote testing would mitigate a significant amount of toxicity and would increase the likelihood that such toxicity would be readily identifiable.

Limitations

Several limitations are apparent.[28] *DPYD* genotyping has a small up-front cost that will be applied to all patients while only benefiting the relatively small number of *DPYD* carriers. However, avoiding severe toxicity in the small population of *DPYD* variant carriers has been found to be ultimately cost-effective and possibly cost saving.[20,29,30] Pharmacogenetic panel testing could spread the cost over multiple medications. Moreover, as genomic sequencing is performed more commonly in patients with cancer at diagnosis, incidental data on *DPYD* variants will be generated, and clinicians will be obligated to act on such data anyway. Treatment delays may occur because of the time taken to generate genotyping results.[31] However, treatment delays and dose adjustments are already common in patients carrying *DPYD* variants who experience toxicity with standard dosing,[13] and turnaround times for genetic sequencing are becoming increasingly more rapid. Preemptive pharmacogenetic testing also obviates this concern. Although dose reductions of anticancer agents are sometimes associated with reductions in efficacy, dose optimization strategies are commonly used in oncology to normalize systemic drug concentrations relative to a traditional patient while maintaining efficacy.[32] In fact, a recent FDA initiative, Project Optimus, is designed to emphasize the selection of doses that maximize both efficacy and safety/tolerability of oncologics. To this end, the FDA should consider that evidence already shows accounting for *DPYD* genotype normalizes pharmacokinetics, toxicity, and outcome of fluoropyrimidines.[33] The FDA has previously proposed a PGx Pyramid Framework and used this mechanism to assess the evidence for HLA/allopurinol, which eventually led to a package insert change to recommend HLA testing.[34,35] Citizen petitions have also led to acknowledgment of the risk to *DPYD* variant carriers in the capecitabine and FU package insert, and other petitions are submitted to the FDA to include pretreatment testing.[36,37] Thus, the FDA has several mechanisms in place to overcome barriers to recommending *DPYD* testing. It would also be reasonable to expect that avoiding fluoropyrimidine overdoses in variant carriers would reduce the use of highly expensive uridine triacetate and costly hospitalizations. Thus, we consider genotype-guided dosing to be dose optimization, not simple dose reduction. Finally, DPD activity is a function of several allelic variants in the gene, and the levels of evidence for these polymorphisms

affecting fluoropyrimidine therapy vary. Although this limitation exists, there are those who are curating the strength of evidence for these alleles for public consumption.[10] Opportunities to understand less common polymorphisms will be increasingly possible if pretreatment *DPYD* testing becomes standard practice.

Recommendations

We recommend that pretreatment *DPYD* variant testing should be incorporated immediately into the standard of care for fluoropyrimidine regimens. Since fluoropyrimidine pharmacokinetic exposure is higher in reduced-function *DPYD* variant carriers, starting at a reduced dose and titrating upward to avoid undue toxicity should be adequate to maximize benefit while reducing risk in patients carrying heterozygous genotypes. Homozygous patients are at unacceptably high risk of fatal toxicity, and fluoropyrimidine therapy should be avoided unless it is absolutely necessary, in which case < 25% of the dose should be administered with DPD phenotyping tests and therapeutic drug monitoring. These methods are already recommended in the CPIC guidelines, and high evidence variants are included therein.[10] Thus, we recommend oncologists order testing before initiating fluoropyrimidine chemotherapy and follow the CPIC dosing guidelines, and the FDA should require updates to the package insert. We recommend that NCCN and ASCO treatment guidelines be modified to reflect the relationship between fluoropyrimidine and toxicity and that a priori testing should be adopted as the standard of care.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

DPYD Testing: Time to Put Patient Safety First

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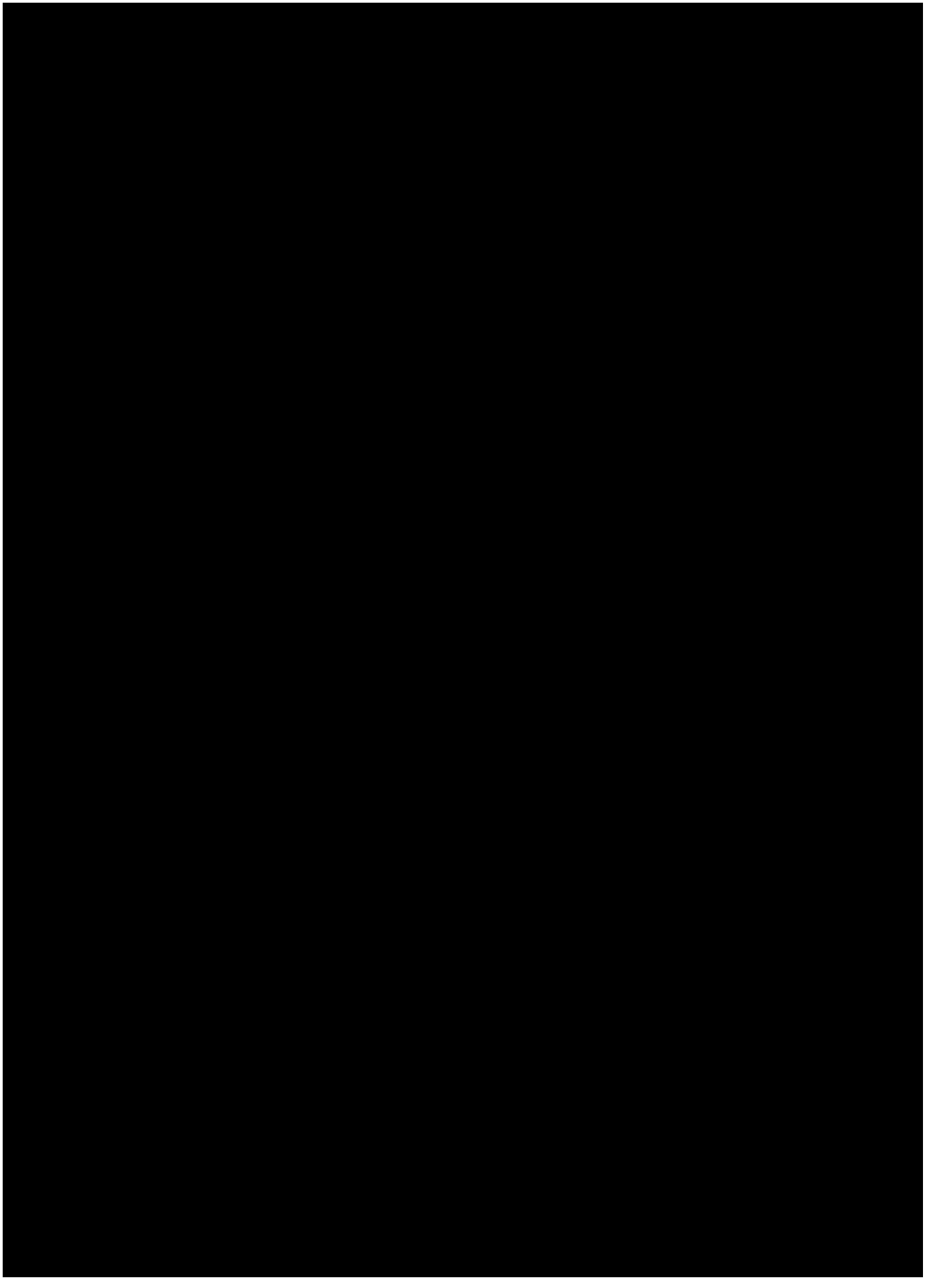
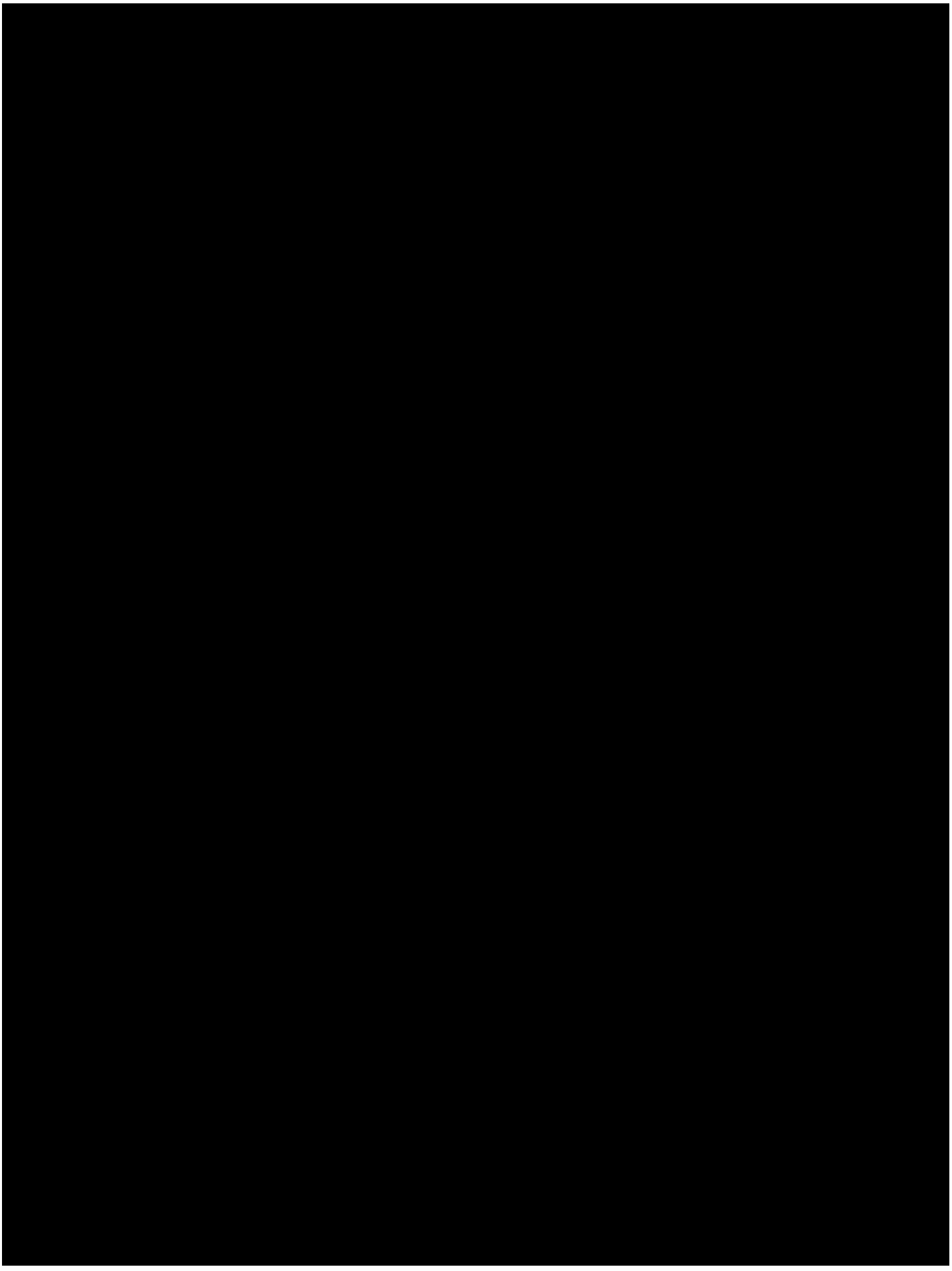
PRECISION MEDICINE ONLINE

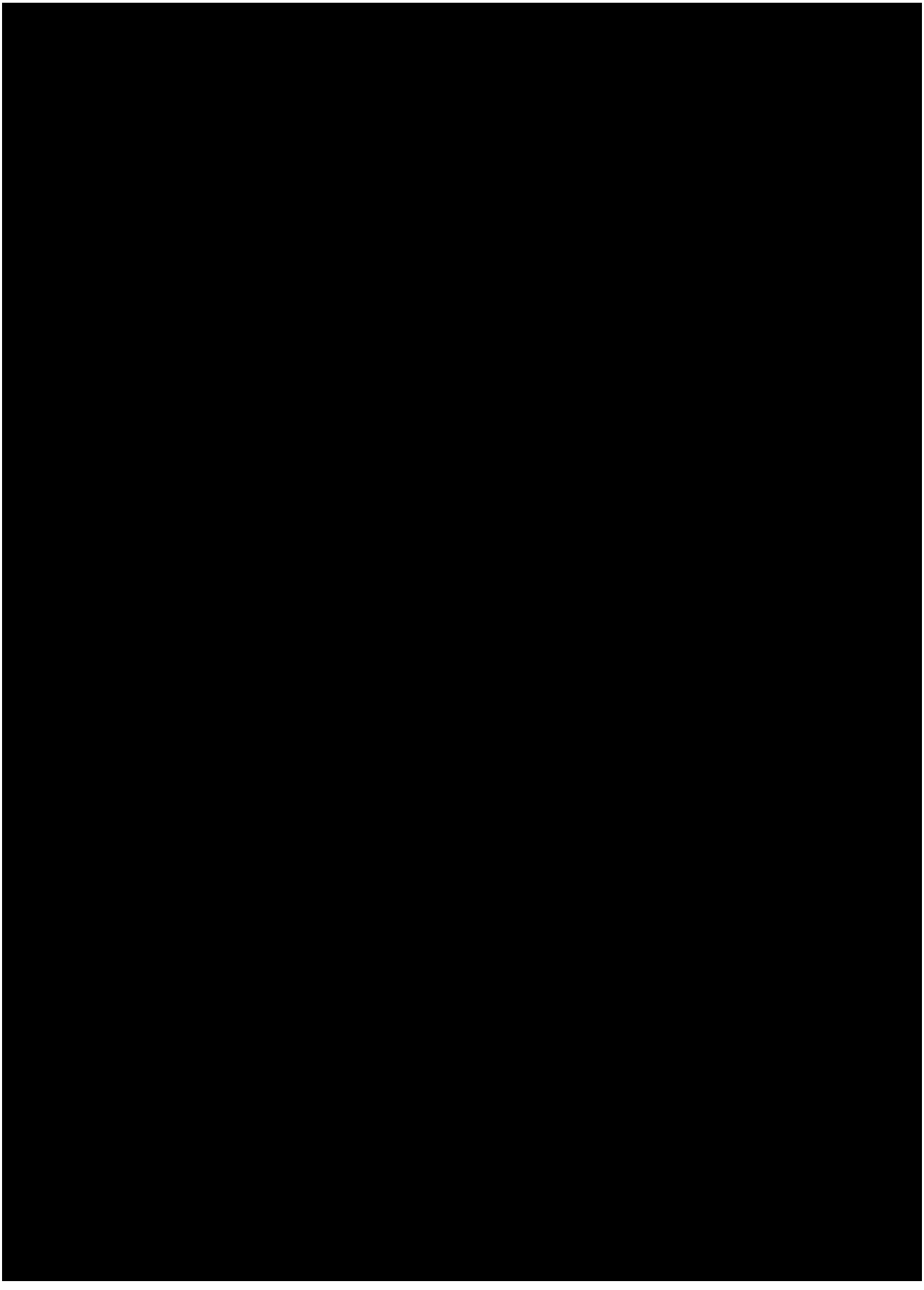
Cancer Centers Nudge Oncologists Toward DPYD Testing as PGx Supporters Push For Guidelines Change

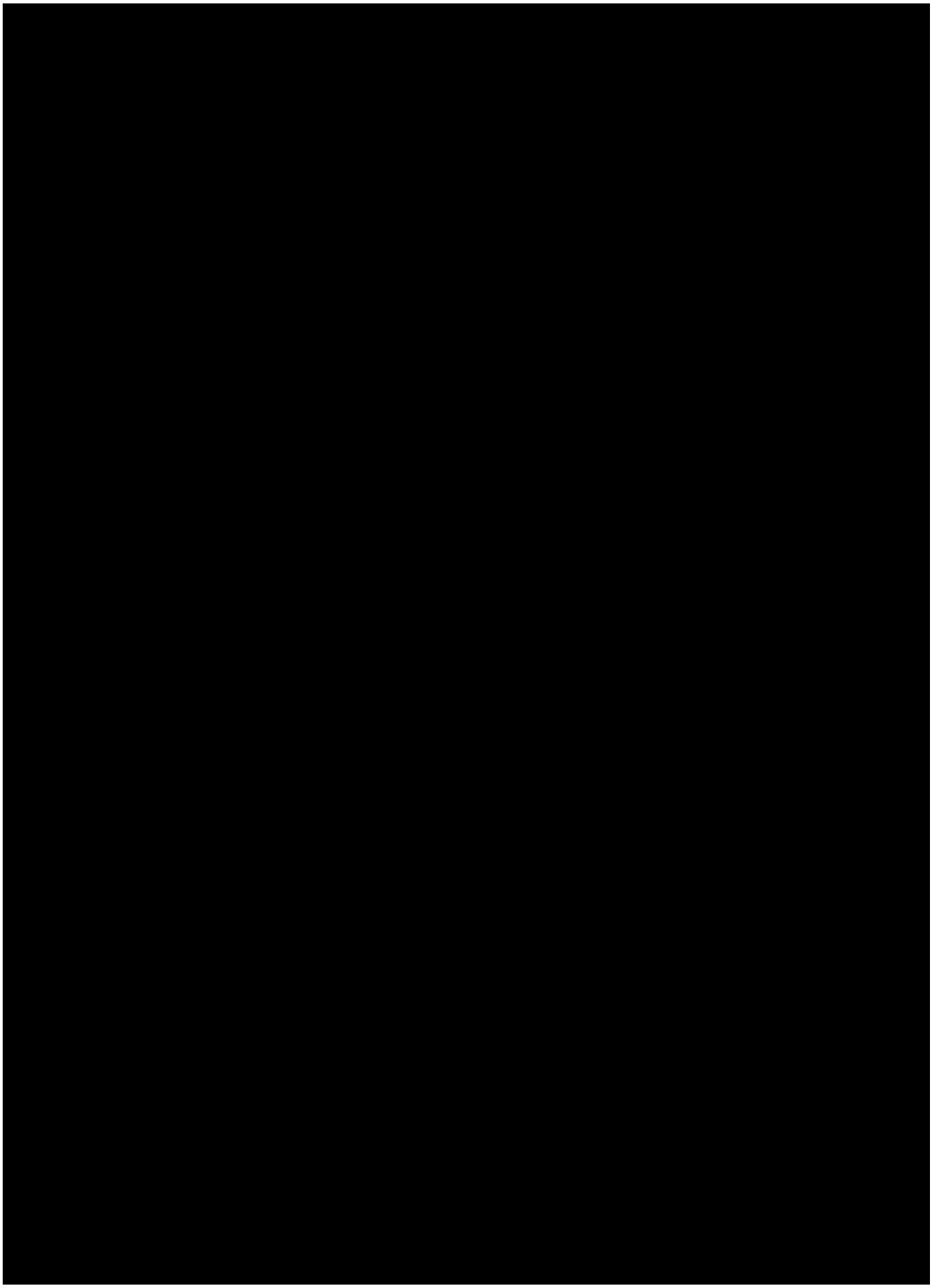
Aug 18, 2022 | Turna Ray

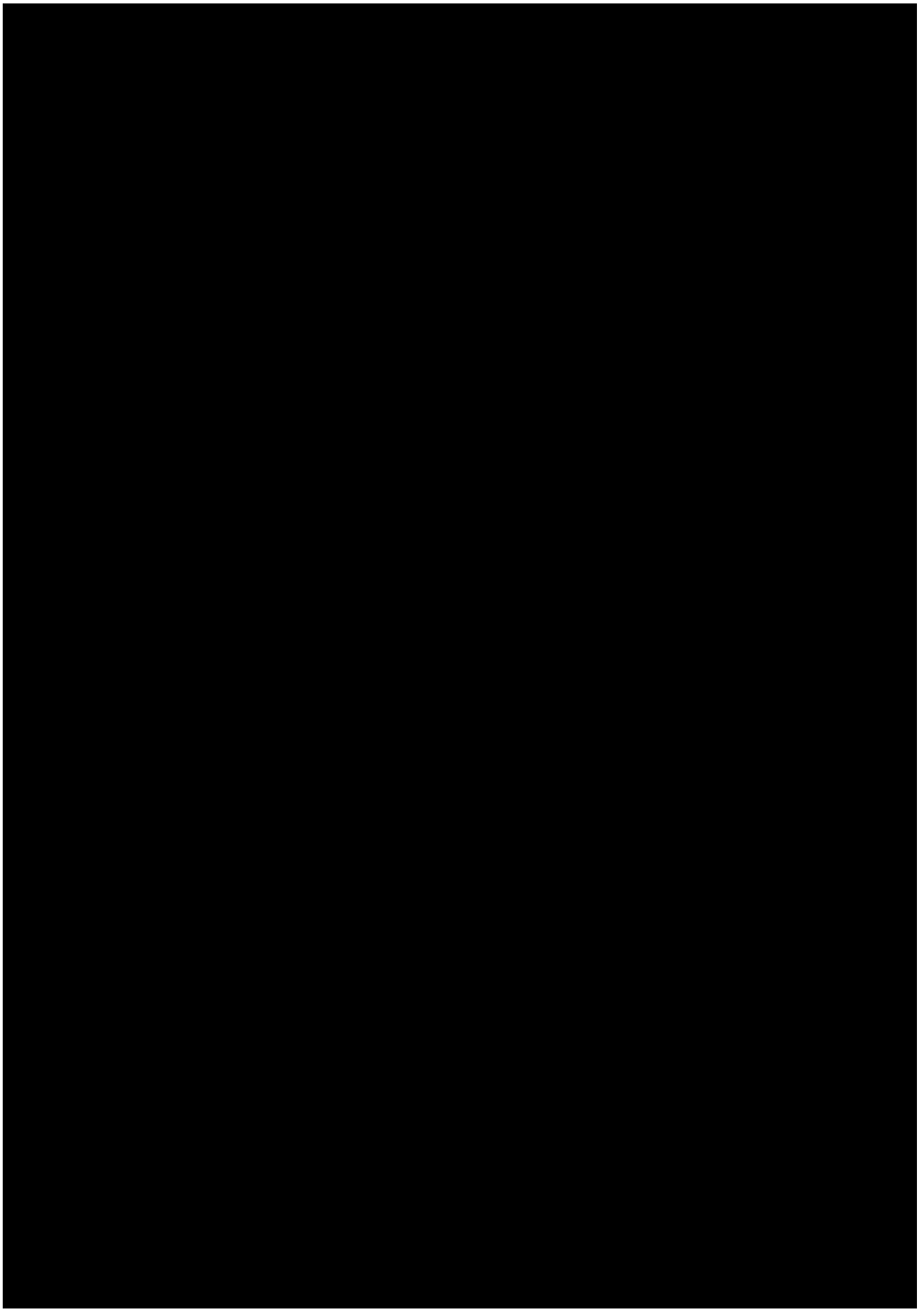
Premium

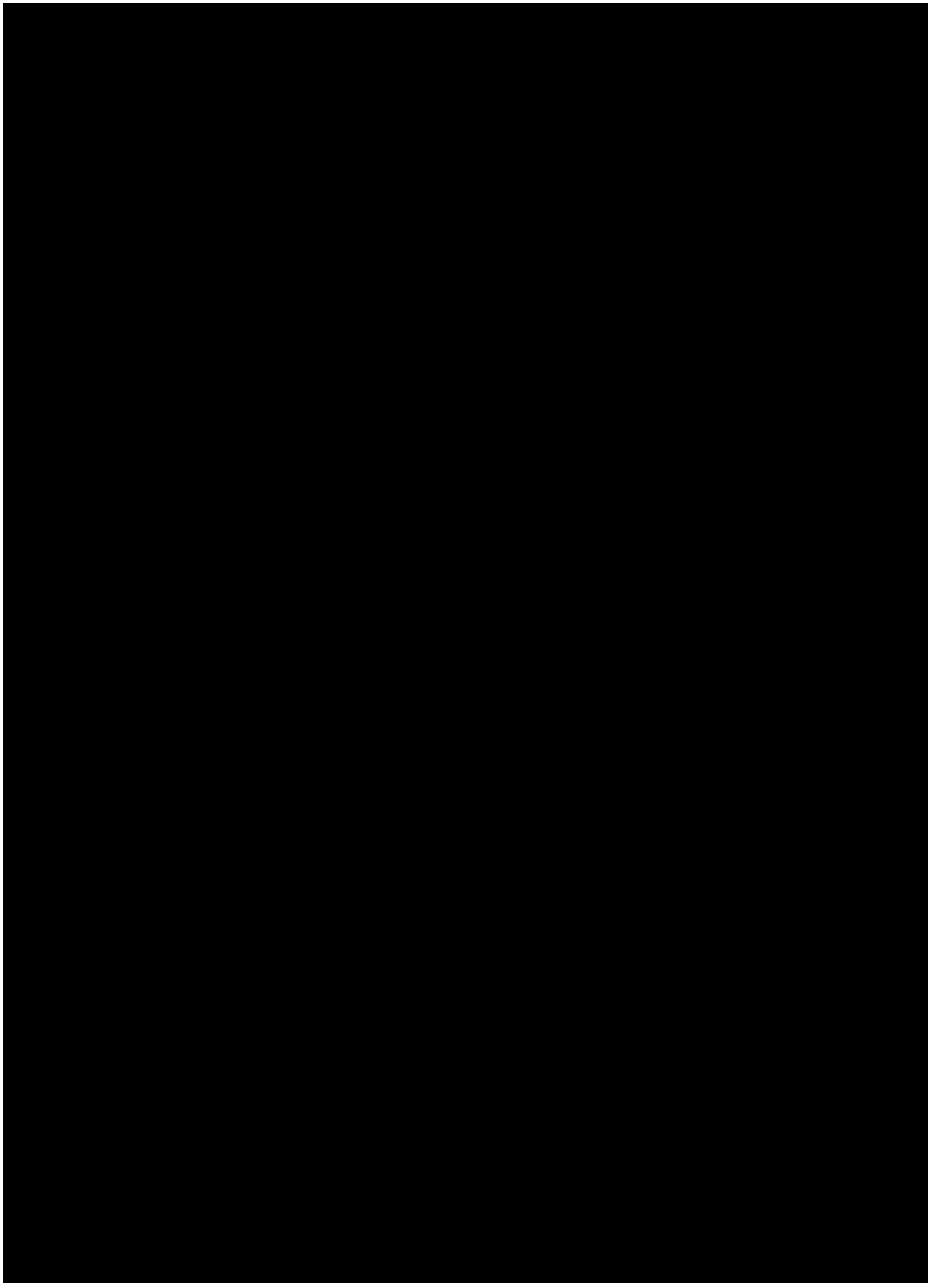


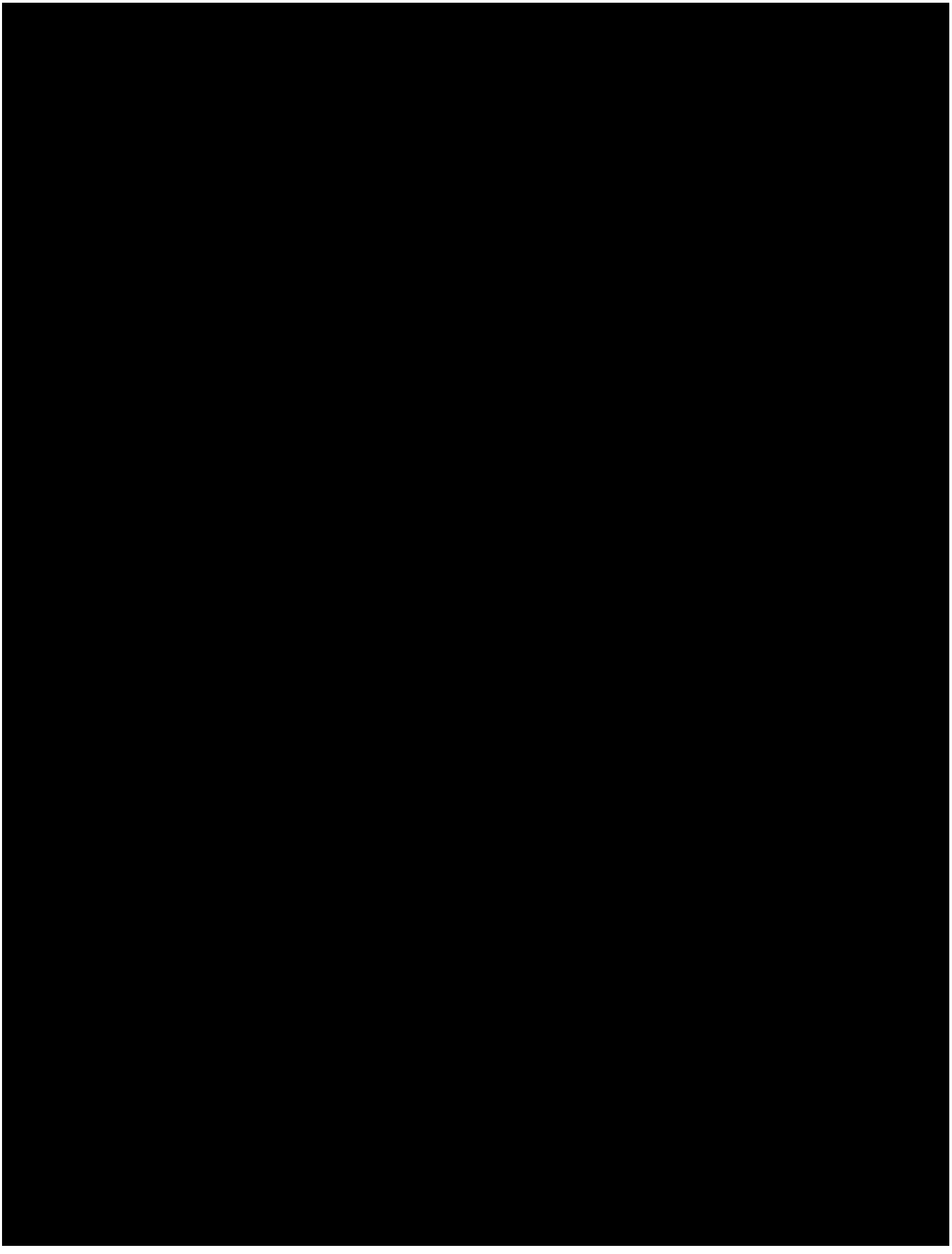


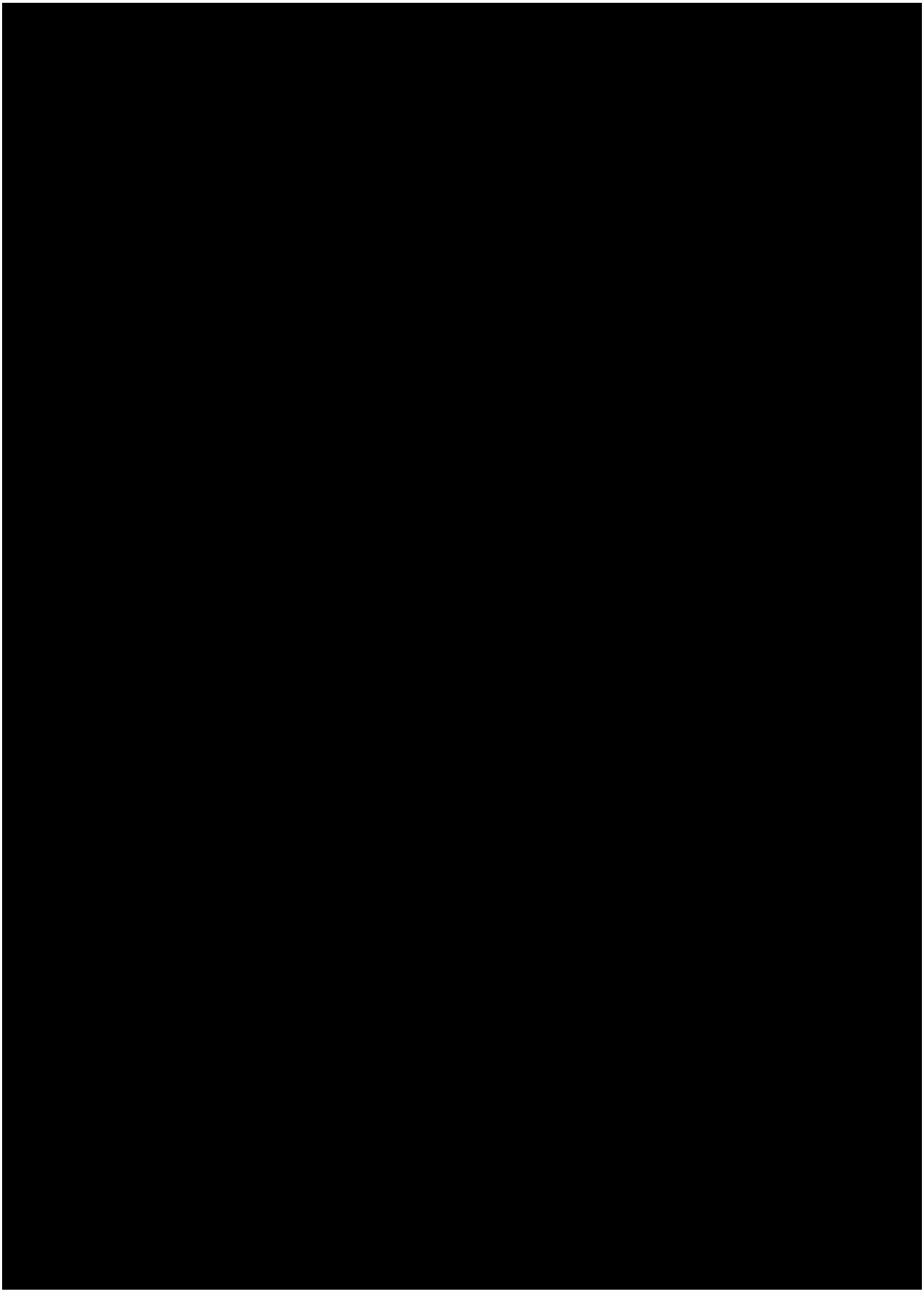


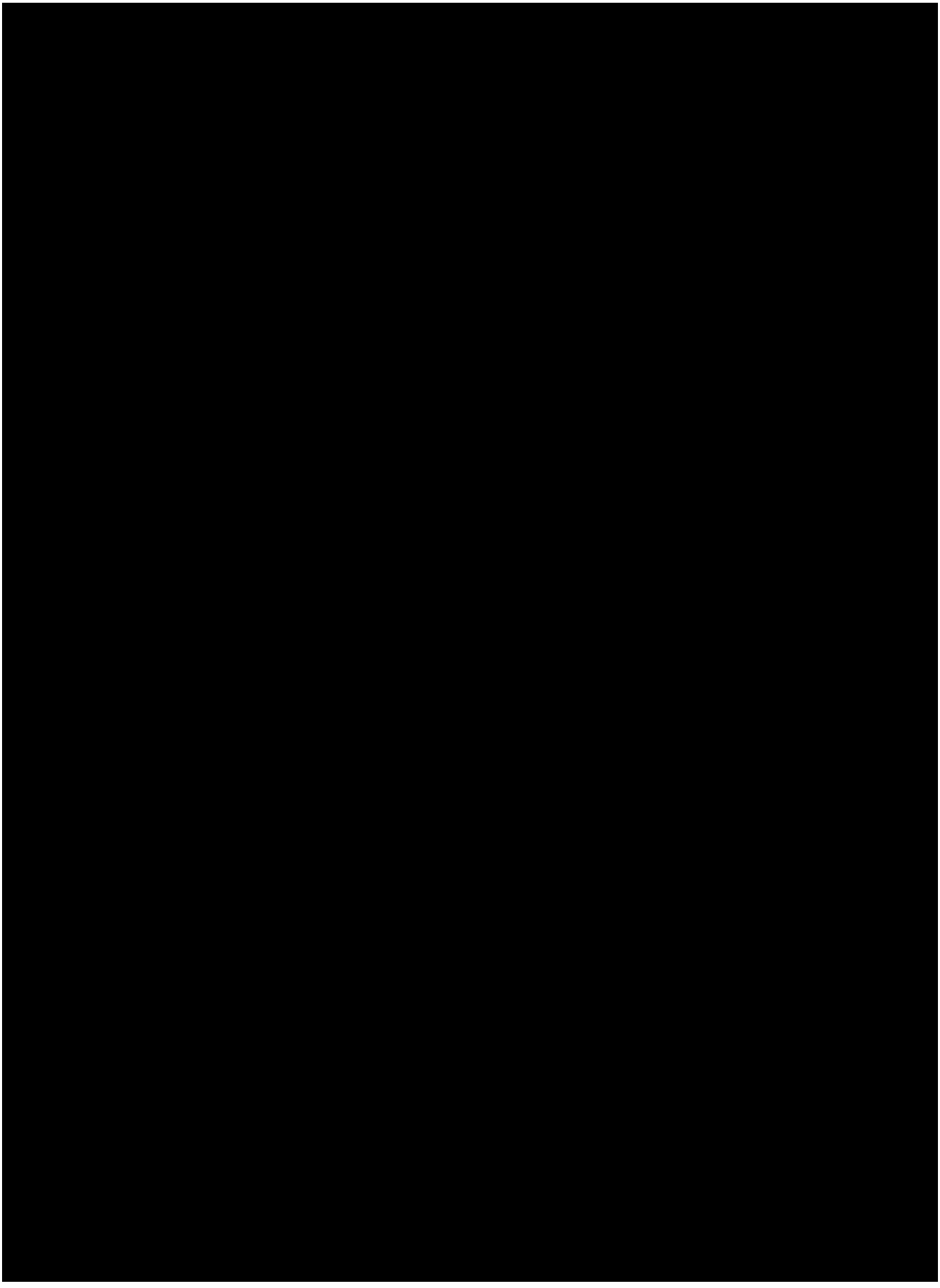


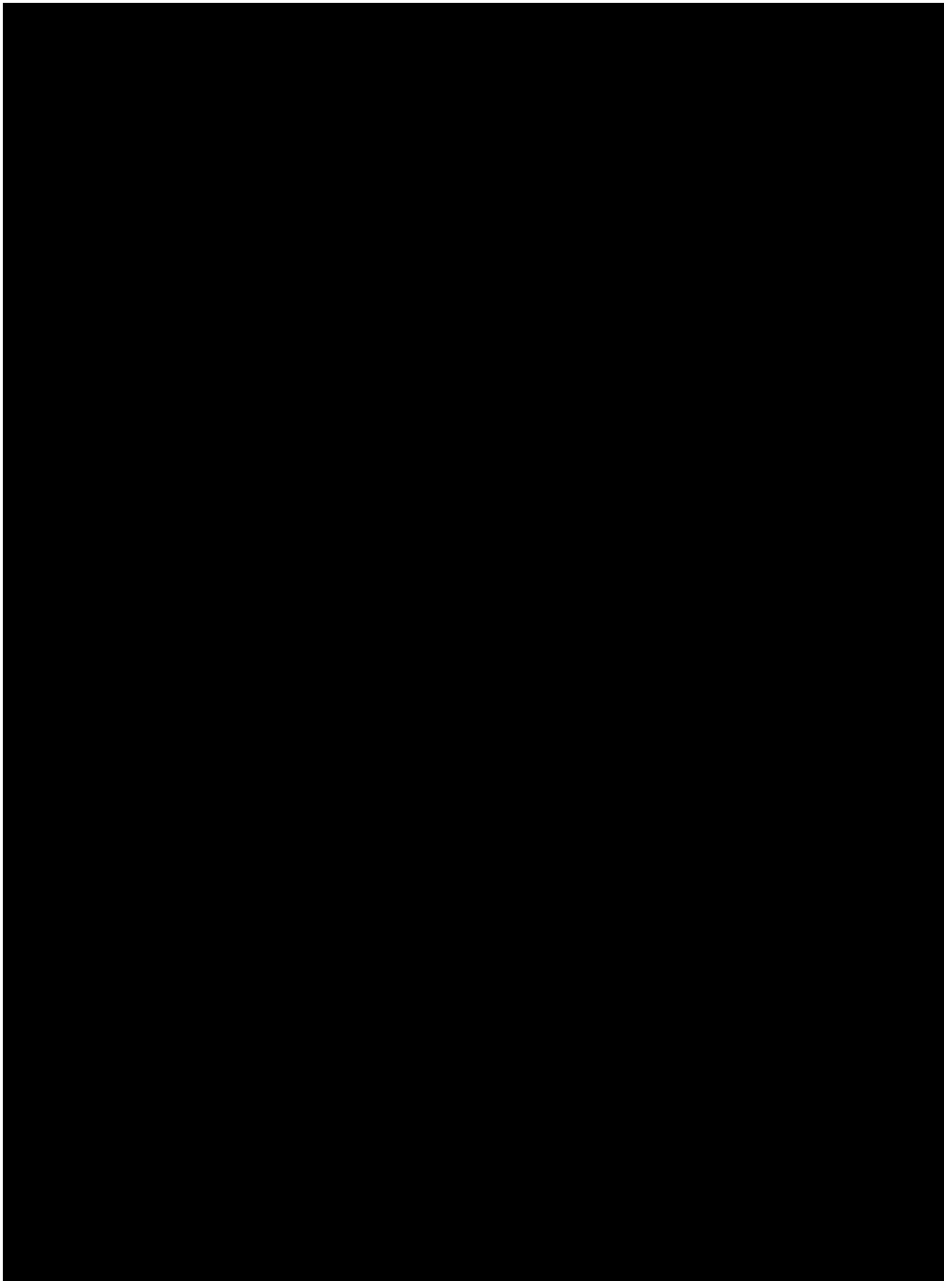












https://pharmgkb.blogspot.com/2022/06/expansion-of-pharmacogenetics-education.html

THE PharmGKB BLOG

Thursday, June 2, 2022

Expansion of pharmacogenetics education agreed as part of lawsuit settlement

Oregon Health & Science University (OHSU) will introduce new educational initiatives on the risks of prescribing the chemotherapy drug capecitabine to patients with DPD deficiency as part of a lawsuit settlement.

The settlement was reached with Joanne McIntyre, whose husband David died as a result of severe capecitabine toxicity. David carried variations in the gene DPYD, which encodes the DPD enzyme. DPD is involved in metabolism of fluoropyrimidine drugs, including capecitabine. Variants in DPYD, such as those that David carried, can inactivate the DPD enzyme, leading to DPD deficiency. Patients with DPD deficiency are unable to properly metabolize capecitabine and other fluoropyrimidines, and are at risk of experiencing severe drug toxicity. In David's case, this toxicity was fatal.

PharmGKB has annotations of several clinical guidelines for capecitabine and DPYD, including those from CPIC and the DPWG. These guidelines uniformly recommend either a dose reduction or selection of an alternative drug in patients with DPD deficiency.

OHSU will hold seminars to educate clinicians on the risks associated with DPD deficiency, how to identify severe capecitabine toxicity in patients and how to administer the antidote. They will also include a module on the topic in their fellowship program and provide a written resource guide to staff in their oncology department. Going forward, patients identified as candidates for capecitabine chemotherapy will be informed of the risks associated with DPD deficiency and, where appropriate, will be offered testing.

We at PharmGKB applaud Joanne's singular dedication to saving patients' lives and OHSU's commitment to implement these changes. Resources on capecitabine pharmacogenomics, including annotations on clinical guidelines for the use of DPYD genotypes in capecitabine prescribing, can be found at the PharmGKB capecitabine drug page.

Posted by Anonymous at 8:59 AM

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